Volume III

HYPERTENSION

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Management

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BACKGROUND

Until about thirty years ago, hypertension was a most depressing disease; although a fair amount was known about the natural history, very little could be done to alleviate its consequences. Patients might be told to rest, to relax, or where relevant to lose weight—but otherwise there was little to offer. In very severe cases, particularly patients with malignant hypertension, heroic surgical procedures like adrenalectomy or sympathectomy were sometimes resorted to, with only limited short-term success.

The great event in the management of hypertensive patients was the development of antihypertensive drugs during the 1950s. Since that time, newer and better drugs have become available, and more and more people have benefited from treatment. There remain, however, some major unanswered questions on who and how to treat, and clinical trials are still under way to resolve some of these problems. The purpose of this chapter is to review the results of the trials available to date.

THE TREATMENT OF MALIGNANT HYPERTENSION

Malignant hypertension is a rare condition; if it is left untreated death occurs within one year from heart failure, renal failure, cerebral haemorrhage, and occasionally myocardial infarction (see Figure 9.1).

When the ganglion blocking drugs first became available, it rapidly became apparent that lives were being saved. The drugs used then—mecamylamine, pempidine, hexamethonium and pentolinium—were fairly intolerable with disabling side-effects but they saved lives dramatically. No placebo-controlled clinical trials were necessary or justified.[1]

BRIEF REVIEW OF THE CLINICAL TRIALS OF NON-MALIGNANT HYPERTENSION

The decision to institute antihypertensive drug therapy in a previously symptomless patient is a major one. The consequences to the patient, his job, his recreation and his general sense of well-being are obvious. Drug therapy should not be instituted unless the clinician is absolutely confident that therapy has been proven to be worthwhile. It has been suggested that hypertension could best be defined as that level of blood pressure where antihypertensive therapy does more good than harm. This pragmatic approach depends on a very careful scrutiny of the evidence that treatment prevents both fatal and nonfatal complications. The various published treatment trials need to be analysed critically, and clinicians must be aware not only of the proven benefits of treatment but also of the areas still to be investigated.

There have been only a limited number of trials of the drug treatment of hypertension in the prevention of vascular

complications. These trials have to be large, with follow-up over many years. Statistically significant results can be achieved only by large multicentre studies, which are expensive and difficult to conduct. A review of these illustrates some of the problems and draws attention to the remaining unanswered questions.

The Chelmsford Study, 1964

The first controlled trial of antihypertensive treatment was conducted in Chelmsford, England in 1964. The control group patients did not, however, receive placebo therapy but were simply followed-up very carefully. Diastolic pressures all exceeded 110 mmHg before therapy.[2] Of the twenty-two men in the study, those treated clearly faired better than controls. In the thirty-nine women, there was little difference in morbidity between treated and controls, but this was partly because blood pressure was not reduced in some of the treated women. When the data for the women were re-analysed on the basis of blood pressure reduced versus not reduced, then clear-cut benefits were found in prevention of stroke and heart failure. Until 1979, this was the only published trial of the treatment of hypertension in women.

The First US Veterans' Administration Study, 1967

This study amongst 143 male armed services veterans largely confirmed the findings from Chelmsford.[3]

The Second US Veterans' Administration Study, 1970

This trial has received a great deal of attention and criticism and the points raised illustrate many of the problems of long-term treatment trials.[4] A total of 380 male

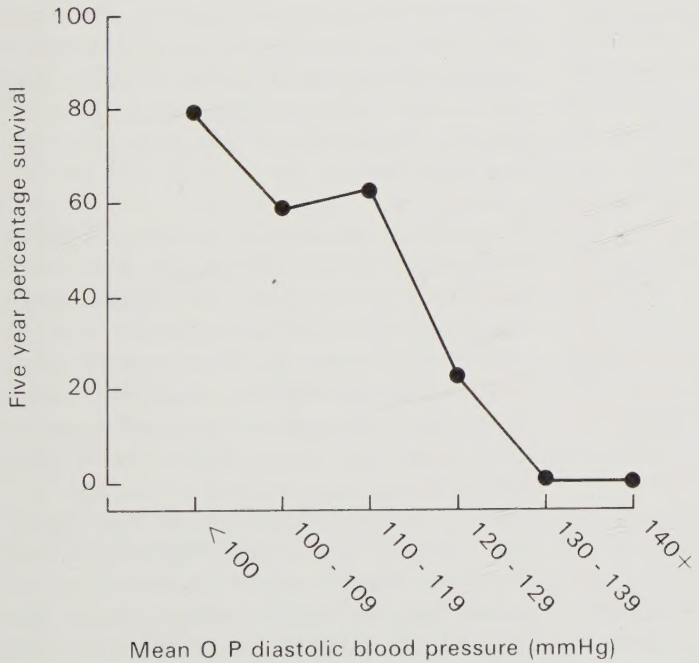

Figure 9.1 Five year survival rate in 200 cases of malignant hypertension, in relation to the accuracy of control of blood pressure at follow-up.

hypertensive patients with diastolic blood pressures ranging between 90 and 114 mmHg were randomly allocated to either an active or a placebo-treated group. Morbid events subsequently developed in thirty-five control group patients and nine actively treated patients. While the benefits of treating cases with blood pressures of 105 mmHg or more were impressive, detailed analysis of the milder cases provides suggestive evidence—but not proof—of the benefits of drug therapy. Of the cases with diastolic pressures below 105 mmHg, 16 per cent of treated patients and 25 per cent of control patients developed morbid events. The greatest benefit was in the older patients who had vascular complications of hypertension before entry.

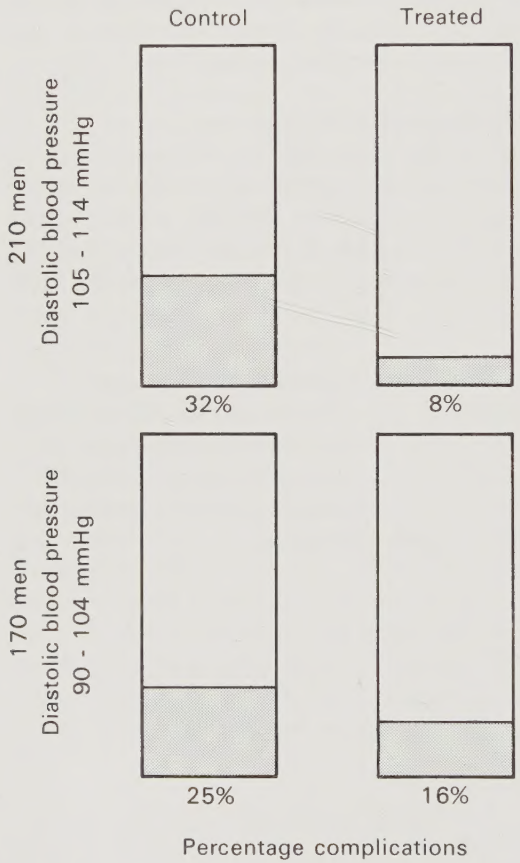

Figure 9.2 Results of the Veterans' Administration trial of the treatment of hypertension (the differences on the lower half of the figure did not reach statistical significance).

The frequency of vascular complication in the control group was surprisingly high, bearing in mind the relative mildness of their hypertension. There are several explanations for this. Firstly, all patients had been admitted to hospital prior to the study and only those whose diastolic blood pressures remained within the range 90 to 129 mmHg during the fourth to sixth day in the ward were entered into the trial. Even very high blood pressures may settle when patients are admitted to hospital. It can be argued that the data from this study do not reflect the results of treating mild hypertensives in the general population. The high proportion of black patients in the VA study (there were 157) may also explain the high frequency of vascular events. Black hypertensives do appear to differ from whites, with many more strokes, although they probably suffer fewer heart attacks (see Figure 9.2).

These early studies of antihypertensive treatment, whilst showing impressive reductions in stroke incidence, were disappointing in their apparent lack of coronary prevention. It is possible that this was because the process of deposition of coronary atheroma was so advanced in these relatively severe hypertensive patients that the introduction of therapy was too late to halt the process. It was argued that coronary prevention might be found if milder cases received treatment at an earlier stage of their disease. It was also considered possible that the use of thiazide diuretics, with their adverse

effects on potassium, glucose and lipids might have meant that the benefits of the reduction of blood pressure were partly offset by a harmful effect of other coronary risk factors.

After the 1970 VA study there was a surprising silence in the world literature and the much needed trials of treatment of mild hypertension did not appear until 1979 and after. There were in the meantime two interesting studies which do contribute to our knowledge of hypertension but do not provide definitive answers.

The Gothenburg Study, 1978

In 1978 a report from Sweden was published in which male hypertensives aged forty-seven to fifty-nine, derived from a single community, were studied.[5] Patients whose blood pressures exceeded 175/115 on two occasions were given active drug therapy. Those whose blood pressures were initially within this range, but which settled, constituted the untreated control group; they were regarded as having somewhat milder hypertension. The most important finding in this study was that the active treatment group suffered not only fewer strokes but also fewer heart attacks than the milder, untreated controls. This study is therefore the first to suggest that antihypertensive therapy might, after all, prevent coronary heart disease. As nearly all treated patients received beta-blocking agents, there was some speculation as to whether this coronary prevention was due to beta-blockers.

The United States Public Health Services Study, 1972

This was a small study of treatment of mild hypertension (diastolic blood pressure 90 to 114 mmHg) conducted in 389 men and women.[6] No significant differences were found in the frequency of strokes or heart attacks between the control and treated patients because there were too few participants to provide definite answers. However, the treated patients developed less radiographic and electrocardiographic evidence of left ventricular hypertrophy.

The Australian Therapeutic Trial of Mild Hypertension, 1979

This was a population-based multicentre trial of the treatment of hypertension in thirty to sixty-nine-year old men and women (see Figure 9.3).[7] Pretreatment diastolic pressures were between 95 and 109 mmHg. There were 3427 participants, half of whom received treatment with thiazide diuretics, with beta-blockers added where necessary, and half of whom received placebo therapy. Randomization and trial methodology were impeccable. After four years the results demonstrated a 30 per cent reduction in mortality in treated patients with a highly significant reduction in strokes. The data for myocardial ischaemia did not achieve statistical significance, although the results were encouraging. The continuation of the trial was considered ethically unjustifiable because strokes were being prevented; the thorny question of coronary prevention was only partially answered. The trial did, however, confirm beyond any doubt that drug treatment of mild hypertension is beneficial in those patients with diastolic pressures of 100 mmHg or more. Below this level the results were encouraging, but no more.

The Hypertension Detection and Follow-up Program (HDFP), 1979

This very large American study has been very controversial on both sides of the Atlantic, and its interpretation remains uncertain.[8] Eleven thousand hypertensive

patients detected at screening surveys in fourteen centres were randomized to two different methods of managing hypertension. It was considered, on the basis of the 1970 VA study, to be unethical to withhold drug therapy from mild hypertensives, even though some sort of trial was considered necessary. So instead half the patients were randomized to attend special stepped care clinics (SC), which were established for the duration of the trial. Blood pressures were treated very aggressively, although therapy was withheld in 24 per cent of patients whose blood pressures fell spontaneously. Drugs were free. The control group (RC) were referred back to the usual medical services. Both groups were rescreened on four occasions during the study and this revealed that 60 per cent of the RC patients were given antihypertensive medication (see Figure 9.4).

There were significant differences in the average blood pressures of the SC and RC groups over the ensuing five years, and at the end of the trial a marked differences in the death rate of the SC and RC patients. SC patients had fewer strokes, fewer heart attacks and less cancer. The organizing committee did not consider it appropriate to apply statistical tests to these data.

The authors considered the trial proved that the drug therapy of hypertension had been validated in all cases where diastolic pressures exceeded 90 mmHg, but this interpretation has been challenged on many grounds. This was not a placebo-controlled trial of drug therapy and so the differences in outcome may have been due to variables other than the differences in frequency of use of antihypertensive drugs. The lower cancer mortality in SC patients suggests that some of the benefits of being in the SC group were due to better general medical care and earlier detection of disease. It is of interest, however, that by the end of the study there was no difference in the rates of cigarette smoking in the two groups.

The HDFP trial is of great interest, and it might be regarded as a validation of the benefits of a form of socialized medicine rather than the value of drug therapy for hypertension. Its results are relevant to the manner of delivering medical care in the United States and it is difficult to extrapolate the findings for other nations with different health care systems.

Population study: 3427 men and women aged 30-69

Diastolic blood pressure: 95 - 109

No of entrants		No of events: Stroke	No of events: Coronary heart disease
1721	Treatment (thiazide)	12	70
1706	Placebo	25	88
	Significance (P)	< 0.025	NS

Figure 9.3 The Australian Study – Second report (1980).

The Multiple Risk Factor Intervention Trial (MRFIT), 1982

This was a large community-based study in which 6428 high-coronary-risk patients were randomly allocated to an intensive multiple-risk-factor programme for blood pressure, smoking habits and plasma lipids.[9] The control group of 6438 people received no active intervention. At the end of the study there was no significant difference in coronary heart disease, strokes or mortality. These negative results are not easily explained, although it was suggested that the employment of thiazide diuretics in the antihypertensive regimes might have aggravated other coronary risk factors including hypokalaemia and hyperlipidaemia. Yet the coronary prevention seen in the Australian and HDFP studies was achieved even with the use of thiazides in the first-line choice of antihypertensive drugs. A more likely possibility is that the control group also received efficient medical care and so did not differ sufficiently from the intervention group.

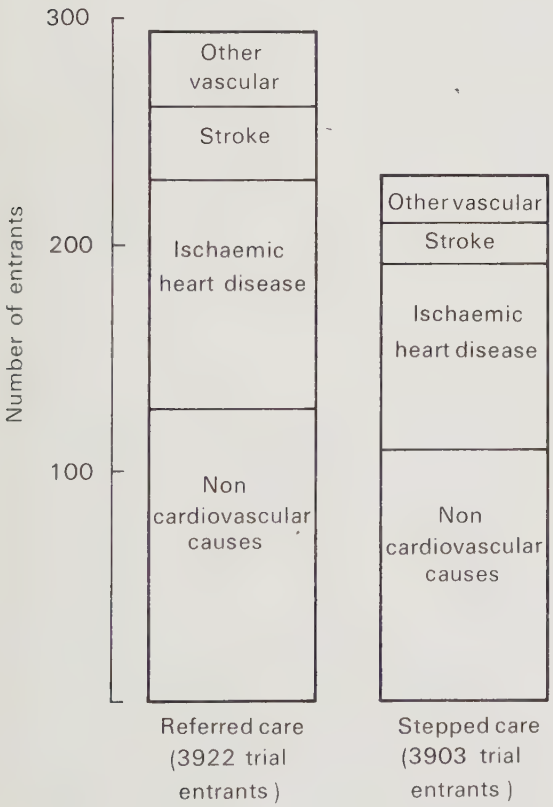

Figure 9.4 Results of the Hypertension Detection and Follow-up Program (Stratum 1) 90–104 mm Hg.

The European Working Party on Hypertension in the Elderly (EWPHE), 1985 and the Hypertension in Elderly Patients Study (HEP), 1986

The topic of hypertension in the elderly is discussed separately in Chapter 15. The EWPHE study compared thiazide therapy with placebo in patients aged sixty years or more (average age seventy-two years). Significant reductions in stroke and in coronary events were reported in treated patients.[10] In the HEP study only stroke was reduced.[11]

The Medical Research Council Trial on Mild Hypertension, 1985

This was a British study of 18,000 men and women. Patients were included if after three visits the diastolic pressure remained between 90 and 109 mmHg.[12] Patients were randomized either to placebo therapy or to active treatment, with either propranolol or bendrofluazide. After 90,000 patient-years, the results were very disappointing. There was a small reduction in strokes, but no reduction in total death rates and no significant effect on coronary heart disease. Thiazides were quite as effective as beta-blockers in preventing complications, and appeared better at preventing strokes. There was some evidence that non-smoking patients receiving beta-blockers faired best in respect of coronary heart

disease. The relatively unimpressive results from the MRC trial are likely to prove a source of controversy for years to come. Already some nihilists have claimed that the MRC results are a mandate to withhold therapy from patients with diastolic blood pressures of between 90 and 109 mmHg. This is a very dangerous interpretation of the trial, which is open to much criticism.

The main worry with the MRC trial is that blood pressures fell after entry into the trial to below 90 mmHg in between one third and one half of cases receiving placebo therapy. These cases might therefore be considered not to have hypertension at all. It is also important to note, however, that 14 per cent of placebo-treated patients sustained a rise in pressure, requiring withdrawal from the trial and the institution of antihypertensive therapy, as their cardiovascular risk would otherwise have been high.

The MRC trial raises many questions on the method of selecting patients for such trials. The act of screening potential entrants may well have caused a rise in blood pressure in a large number of people. The trial does demonstrate very convincingly that it is wrong to institute drug therapy in mild hypertensives on the basis of only three slightly raised blood pressure readings. Mild hypertensives require a longer period of assessment without therapy, and at this time non-pharmacological therapy can be attempted (see Chapter 10). We need more information on how to select out those mild hypertensives whose blood pressures will fall from those who will have sustained hypertension requiring therapy. The presence of minor ECG abnormalities (see Chapter 14) may be a useful indicator of more serious hypertension.

The MRC trial results must be considered in the light of the other published studies of the treatment of mild hypertension, including the Australian trial and the EWPHE report. The benefits of treating mild hypertension over five years are not dramatic, as may be expected. The clinician must in the final analysis make his own judgment as to which mild hypertensives he will treat with drugs and whom he will simply counsel about associated coronary risk factors, particularly cigarette smoking. All patients do, however, need careful follow-up, as blood pressures tend to rise with age and many mild cases will develop severe hypertension if left untreated.

The United States Systolic Hypertension in the Elderly Program (SHEP)

This trial, initiated in the mid 1980s, has been designed to investigate the benefits of antihypertensive therapy in patients who have 'isolated systolic hypertension'.[13] This should provide useful information on the correct method of managing patients who have normal diastolic pressures but raised systolic pressures.

The Heart Attack Primary Prevention in Hypertensives (HAPPHY) Study and the International Projective Primary Prevention Study in Hypertension (IPPPSH)

These two international multicentre studies are designed to test whether patients randomized to receive a beta-receptor blocker develop fewer complications than those receiving a thiazide diuretic.[14,15] Preliminary results of the IPPPSH study suggest that beta-blockers are superior to thiazides only in coronary prevention in males who are nonsmokers. This confirms the findings of the MRC trial of an important cigarette smoking beta blockade interreaction. It is possible that

in future these drugs will be considered to be first line therapy only in nonsmokers. More information is necessary on this point, particularly in relation to the effects of smoking on the metabolism of antihypertensive drugs.

GUIDELINES ON WHOM TO TREAT WITH ANTIHYPERTENSIVE DRUGS

Clinical trials provide information about the benefits or otherwise of treating groups of patients with various levels of hypertension. They cannot, however, provide all the answers about individuals. For the clinician the most useful data is on the extent to which the risk to the patient — both relative and absolute — may be altered. For example, the Australian National Blood Pressure Study demonstrated a 30 per cent reduction in mortality as a result of treatment. While this sounds impressive, the same data presented differently show that to prevent thirty-one heart attacks and strokes, 1721 patients need to receive drug therapy for up to five years. In that trial 1690 patients received treatment but derived no absolute benefit during the five years of the study. Similarly, the MRC trial reported that to prevent one cardiovascular event it is necessary to treat 625 patients for one year. It is likely, however, that more people would benefit over a longer period as blood pressures rise with age, and the development of more severe hypertension would be prevented. The pay-off of one complication prevented for 625 patients treated may seem very unimpressive. This statistic does not, however, take into account the many people whose blood pressure fell with placebo, and is also based on men and women combined. If men are examined alone, the number of patients who benefit over five to ten years becomes much higher.

The Australian study also showed the risk to a hypertensive patient, when his blood pressure is normalized by antihypertensive drugs, does not completely return to normal. His or her prognosis is still adverse when compared with that of a person whose blood pressure is normal without drugs. This is not particularly surprising; if hypertension and its sequelae take many years to develop, it would be unlikely that drug therapy delivered once blood pressures have reached 90 to 109 mmHg would totally abolish the excess risk.

THE PRESENT STATE OF KNOWLEDGE OF THE BENEFITS OF TREATING HYPERTENSION

From the above studies, a reasonable conclusion is that in patients under the age of seventy-five, if the diastolic blood pressure consistently exceeds 100 mmHg after three consecutive screening visits, blood pressure reduction is worthwhile. Strokes and heart failure are prevented, and there is some evidence now of coronary prevention as well. The WHO and the International Society of Hypertension have stated that this threshold should be at 95 mmHg rather than 100 mmHg.[16] It is also important to note that in treated hypertensive patients, the quality of control of the blood pressure is a better predictor of outcome than the severity of hypertension prior to therapy. This means that the efficient delivery of antihypertensive therapy remains a high priority.[17]

The information available for patients whose diastolic pressures are between 90 and 99 mmHg is still controversial. However, if after six visits, pressures remain within this range in spite of non-pharmacological measures, then antihypertensive drug therapy is justified. Those people whose blood pressures settle should not receive therapy but they must

be followed up as many will sustain a rise in pressure over the ensuing years, so that treatment becomes necessary.

It would be nice if more information were to become available to help the clinician decide whom he *must treat*, whom he *may treat* and from whom he may choose to *withhold treatment*. The following guidelines reflect our present knowledge.

Who must receive treatment

1. All patients below the age of seventy-five whose diastolic blood pressure is consistently more than 100 mmHg. In patients between the ages of 75 and 85, therapy is justified if the diastolic pressure exceeds 110 mmHg.
2. All pregnant women with diastolic pressures greater than 100 mmHg (see Chapter 16).
3. Patients whose diastolic pressures remain between 90 and 99 mmHg, but who have a high risk of death by virtue of other factors, for example, cigarette smoking and high blood cholesterol levels and possibly bad family history.
4. Patients with ECG or chest x-ray evidence of left ventricular hypertrophy, whose diastolic pressures exceed 90 mmHg or whose systolic pressures exceed 180 mmHg.

Who must not receive treatment

1. People with diastolic pressures below 90 mmHg.
2. Patients over the age of eighty-five unless they have diastolic pressures above 110 mmHg.
3. Patients who have suffered a stroke within the previous few weeks. After this period, however, antihypertensive therapy is worthwhile in presenting recurrences.
4. Stroke survivors with diastolic pressures below 100 mmHg.

Who may be left untreated – but with careful review

1. Patients with a diastolic blood pressure of 90 to 99 mmHg, who have low risk, i.e., nonsmokers with no abnormality of plasma lipids and a favourable family history, and whose pressures settle.
2. People who have intolerable drug side-effects despite all attempts to find a suitable regime and whose diastolic blood pressures are below 105 mmHg off therapy.
3. Very anxious patients in whom the clinician suspects or knows that blood pressure is usually normal when at home, and in whom there is no evidence of end-organ damage and no left ventricular hypertrophy on the ECG. In these people it may help to obtain some form of ambulatory home blood pressure recordings to confirm whether they do have a 'blood pressure clinic-induced hypertension'.

Men and women

While, for a given level of blood pressure, women have a lower risk of death than men, blood pressure levels remain a potent predictor of risk (see Chapter 3). The benefits of antihypertensive drug therapy in women are as important as in men, and the same therapeutic thresholds apply.

Black patients

Hypertension may be commoner in black people compared with whites in Britain as well as in the USA (see Chapter 3).

However, there is only unconvincing evidence that black patients, for a given level of blood pressure, have a higher risk of death than whites. Treatment trials have shown that blacks benefit as much as whites from antihypertensive therapy. Beta-receptor blockers and angiotensin-converting-enzyme inhibitors on their own may be slightly less effective. Thiazide diuretics and calcium-entry antagonists may, by contrast, be more effective in blacks than in whites.

The topics of hypertension in the elderly, in children and in pregnant women are dealt with elsewhere. Similarly, hypertension in the presence of established vascular complications is discussed in Chapter 14.

PRACTICAL POINTS

- In patients below the age seventy-five diastolic blood pressure above 100 mmHg should be reduced.
- The quality of care of hypertensive patients is critical.
- Controlled trials on the value of drug therapy have shown treatment has a beneficial effect in preventing stroke and possibly coronary heart disease.
- Efficient follow-up must be arranged for all cases to ensure that the therapeutic goals are achieved.

10
Non-drug control of blood pressure

BACKGROUND

When population screening surveys are conducted in Western countries 20 to 30 per cent of adults are found to have high blood pressure as defined by a diastolic pressure greater than 95 mmHg or a systolic pressure greater than 160 mmHg (see Chapter 1). An increased risk of cardiovascular disease is also present in those whose blood pressures are in the upper half of the normal distribution (i.e., around 50 per cent of the population), when compared with people in the lower part of the distribution. While many of these blood pressures tend to fall on rechecking, the prospect of 20 to 30 per cent of the population swallowing blood pressure lowering drugs must be viewed with alarm. Surely a new approach taking heed of the following issues is needed:

1. Can we prevent high blood pressure developing?
2. Can we lower pressures by altering our patients' lifestyles?

Since we are primarily concerned here with practical management, this chapter will be devoted to the second of these questions.

The immensity of the problem of treating hypertension on a population basis with drugs has forced a search for alternative ways of lowering blood pressure. There is now exciting evidence that blood pressure can be lowered by non-pharmacological means. However, many of the studies showing this are not well controlled and have small numbers of participants and a shorter duration than many drug-based trials. The subject of non-pharmacological blood pressure reduction is sometimes confused by enthusiasts who believe their particular method of lowering blood pressure is the most effective one. In general, there is an inverse relationship between evangelical zeal and real evidence. Results are often difficult to interpret because simple observation of the patient in the clinic over weeks or months may also cause a fall in pressure.

OBSERVATION

Repeated measurement during follow-up will cause a fall in blood pressure. This was best illustrated in the Medical Research Council Trial of Mild Hypertension (see Chapter 9). A group of patients on drug treatment were compared with a similar group on placebo and a similar group who were observed without even placebo tablets. All were seen at regular intervals during the trial.[1] There was a fall in blood pressure in all three groups. In the group receiving drug treatment it was only just significantly greater than in the other two. Placebo therapy did not have an additional effect compared with follow-up alone. The fall in blood pressure was therefore due simply to observation. Many other studies have shown similar results. The time that the blood pressure takes to fall in relation to

the number of observations has not been established. However, three important conclusions can be drawn from these studies:

1. Patients with mild hypertension must always be observed for at least three months, and their blood pressure measured on three or more occasions, before any form of therapy is initiated.
2. If the initial three-month observation period is combined with some other manoeuvre such as weight reduction, salt restriction, correction of alcohol overuse or relaxation therapy, the blood pressure lowering may be falsely ascribed to that intervention.
3. In trials of non-pharmacological methods of lowering blood pressure an appropriate control group or a crossover with a placebo is necessary to ensure the effect is due to the intervention and not to the repeated measurement of blood pressure.

(a)	Minerals
	Sodium
	Potassium
	Calcium
	Magnesium
(b)	Saturated fat/polyunsaturated fat
(c)	Fibre intake
(d)	Calorie content/carbohydrate intake
(e)	Vegetarian diet
(f)	Alcohol
(g)	Caffeine

Table 10.1 Factors in diet that may influence blood pressure.

An important but unanswered question is whether the fall in blood pressure that occurs with observation alone is of benefit to the patient. Presumably the mechanism is that the patient becomes more familiar with the techniques of measurement and is therefore more relaxed. This also points to the possibility that at home some patients may have lower blood pressures than when seeing the doctor.

ALTERATION OF DIET

There is increasing evidence that altering the diet in Western countries may lower blood pressure. Table 10.1 summarizes the factors set out here.

Sodium restriction

We all eat very large amounts of salt, consuming ten to fifty times the amount eaten during man's evolution. There is overwhelming evidence in animals and good circumstantial evidence in man that a high sodium intake is an important initiating factor for high blood pressure, if not an underlying cause of essential hypertension.[2]

It is likely that the mechanism whereby sodium restriction lowers blood pressure in hypertensive patients is different from the longterm mechanism whereby a high salt diet may cause a rise in blood pressure in the population. The clinician is clearly more concerned with the possible benefits to his patients than with the implications of a high salt intake for the whole population.

Severe sodium restriction

Ambard and Beaujard, two French nephrologists of the early 1900s, were the first to point out that restriction of sodium chloride in the diet lowered blood pressure in patients with chronic renal failure and hypertension.[3] This early work was largely forgotten until Kempner in

the days before drugs were available had the idea of reducing protein intake in severe hypertension.[4] He developed a rice and fruit diet that was low in protein but also very low in sodium and rich in potassium. This was found to be effective in malignant hypertension and in patients with very high blood pressures. However, the diet, which consisted of plain boiled rice and fruit, was very monotonous so patients found it difficult to tolerate. With the development of the thiazide diuretics in the 1950s, this severe form of sodium restriction was largely abandoned.

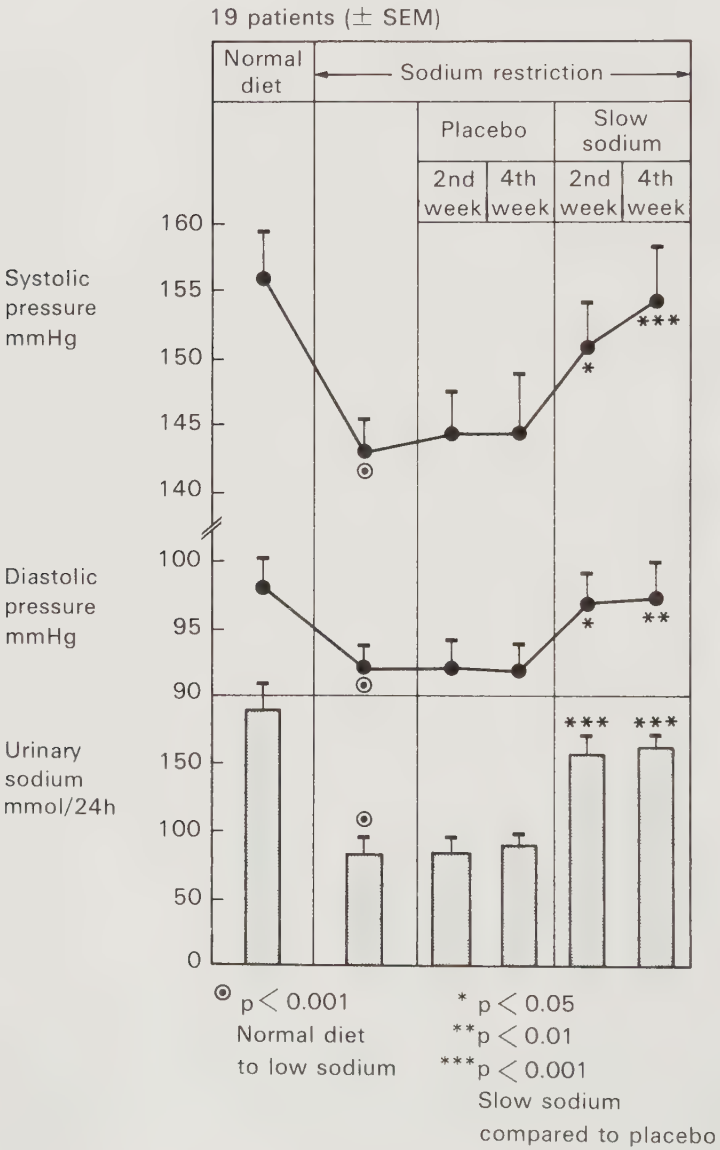

Figure 10.1 The effect of moderate sodium restriction on blood pressure and urinary sodium excretion in a double blind study using placebo and slow sodium tablets.[5]

Moderate sodium restriction

There is now increasing evidence that more modest restriction of sodium intake may lower the blood pressures of hypertensive patients (see Figure 10.1).[2,5] It may also be additive to antihypertensive drug therapy and limit the fall in plasma potassium caused by thiazide diuretics. In most studies sodium intake was reduced by about half and the fall in diastolic blood pressure was between 5 and 10 mmHg; an effect comparable to that of a diuretic or a beta-blocker.

Sodium restriction, in the short term, may be more effective in patients with high blood pressure when compared with normotensives (see Figure 10.2). When dietary sodium is restricted, there is a loss of body sodium resulting in a reduction in extracellular fluid and blood volume. This stimulates renin release and the formation of angiotensins II, which in normotensive subjects may largely prevent any fall in pressure. In hypertensives there is less rise in renin and therefore sodium restriction does cause a fall in blood pressure.[2] More studies are needed to look at the longterm effects of salt restriction and to identify which patients respond best.

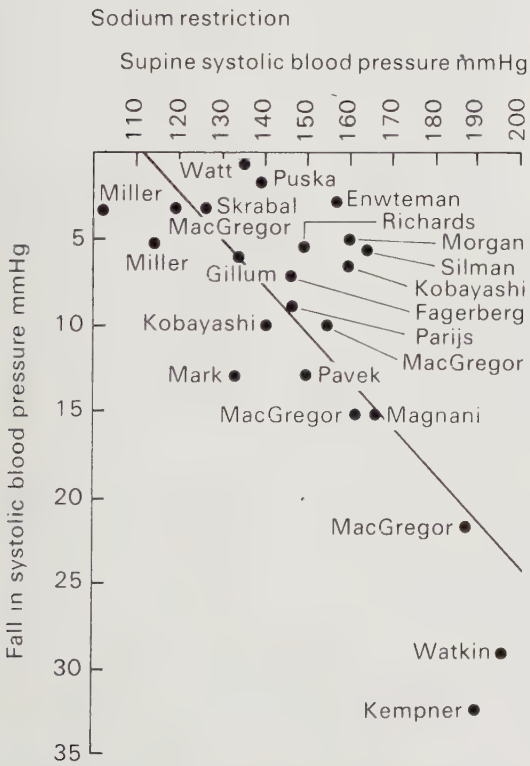

Figure 10.2 Fall in supine systolic blood pressure with sodium restriction plotted against pretreatment supine systolic blood pressure in different places.

Assessment of sodium intake

A dietary history does not give a very accurate estimate of sodium intake. This is because it is difficult to quantify the amount of salt added during cooking or at table. The best method is to measure the amount of sodium excreted in the urine as this represents about 90 per cent of dietary intake. Sodium consumption varies widely from day to day and urinary sodium excretion follows these changes. There is some confusion as to how many urine collections are necessary to reflect the average sodium intake of an individual patient. The collection of two consecutive twenty-four-hour urine samples gives a reasonable approximation as to whether a patient is eating large amounts of sodium (i.e., more than 200 mmol/day, equivalent to approximately 11 g sodium), an average sodium intake (around 150 mmol/day, approximately 9 g), or a low sodium intake (less than 100 mmol/day; approximately 6 g).

The collection of twenty-four-hour urine specimens requires some organization, but it is not as difficult as has been claimed if the patient is given clear written instructions (see Chapter 8).

How to cut sodium intake

At present all patients with high blood pressure should be told:

1. Not to add salt to the food at the table
2. To avoid or severely limit the addition of salt in the preparation of food; the person who cooks for the patient should be counselled
3. To avoid processed foods that have a very high sodium content, for example, ham, bacon, sausages, hamburgers and other processed foods
4. To avoid potato chips, salted peanuts and other sodium-rich snacks.

These four simple steps can halve sodium intake in most patients.[6] To reduce it further means cutting out many other processed foods and more detailed instructions are required, preferably from a dietitian. In some countries the labels on packaged and processed foods carry information about their sodium content.

It is especially difficult to restrict sodium intake if food is eaten regularly in a canteen or a restaurant. Fast foods and Chinese takeaway meals have a particularly high sodium content.

Increasing dietary potassium

Potassium was used as a diuretic in the early 1930s in patients with heart failure and it was suggested that an increase in potassium intake might lower blood pressure. These observations were not pursued until evidence from rats showed that increasing dietary potassium largely prevented the pressor effect of a high sodium intake. Very few studies have been done in man. So far they suggest that on a normal diet containing around 150 mmol of sodium per day, an increase in potassium intake does have a small but significant blood pressure lowering effect.[7] There is also some epidemiological evidence (see Chapter 3) suggesting that a low potassium intake is related to the prevalence of high blood pressure in a community. However, none of the evidence is as impressive as for sodium restriction and no longterm studies have been reported.

The antihypertensive effect of a high potassium diet may not be additive to the effects of sodium restriction but increasing potassium consumption through a higher intake of fresh fruit and vegetables makes patient compliance with sodium restriction easier. In addition, an increase in fruit and vegetable consumption may help reduce saturated fat intake and increase the fibre content of the diet. All these steps may be of benefit in the longterm prevention of atheroma.

An increase in potassium intake is, however, contraindicated in patients with hypertension with severe renal failure.

1. **Do not add salt** to cooking or at table
2. **Avoid very salty foods**, eg, bacon, ham, cheese and limit processed foods with high salt content
3. **Eat less fat** — if necessary substitute polyunsaturated for saturated fat
4. **Eat more fresh fruit and vegetables**

Table 10.2 Simple dietary guide for patients with high blood pressure.

Salt substitutes

The use of salt substitutes containing potassium rather than sodium chloride has been advocated both to help compliance with salt restriction and to increase potassium intake.

There are now many combinations on the market of sodium and potassium in so-called salt alternatives. These cannot be recommended in the treatment of high blood pressure as they contain appreciable amounts of sodium. Potassium salts should not be given to patients with renal failure.

Calcium

The epidemiological evidence relating calcium to blood pressure is discussed in Chapter 2. High blood pressure may be related to a low calcium intake and one clinical study has shown that increasing dietary calcium intake caused a surprisingly large fall in blood pressure.[2] Further well controlled double-blind studies are needed before any recommendations can be made, particularly as the main source of calcium in the diet is in dairy products, which are high in saturated fat, cholesterol and sodium.

Magnesium

Magnesium, like potassium, is an important regulator of the excitability of cell membranes and is found in many foods. Magnesium sulphate used to be given intravenously in pre-eclamptic toxaemia and was an effective blood pressure lowering agent. Magnesium supplements, when given to patients with high blood pressure who were already receiving a diuretic, appeared to cause a further fall in blood pressure. However, in a recent double blind study, magnesium supplements had no effect on blood pressure when compared with placebo.[8]

Saturated fat and polyunsaturated fat

There is some evidence from Scandinavia that substituting saturated fat intake with polyunsaturated fat may lower blood pressure in both hypertensive and normotensive subjects.[9] Further controlled studies are needed but there are other reasons for believing that reducing the saturated fat content of the diet may be beneficial. There is good evidence that high blood cholesterol levels and the low density lipoprotein (LDL) that carries cholesterol are important risk factors for arterial disease. High plasma cholesterol levels greatly increase the risk for a given level of blood pressure. The evidence that lowering saturated fat intake is beneficial is not yet conclusive. On the other hand, it is unlikely to be harmful and will reduce calorie intake, helping with weight reduction. Polyunsaturated fats are predominantly found in vegetable oils such as sunflower, soya bean and corn oil and many fish oils.

Dietary fibre

This consists of complicated carbohydrate substances that are not absorbed but decrease intestinal transit times and are useful in the prevention of constipation. They have also been claimed to reduce the incidence of colonic cancer as well as other gastrointestinal problems. One study from Southampton has shown that increasing the dietary fibre content did have the effect of lowering blood pressure.[10] It is not clear whether this was due to a direct effect of the increase in fibre in the diet or to a concomitant alteration in sodium intake or absorption. Increasing fibre in the diet with greater consumption of fruit, vegetables and wholemeal cereal products is probably beneficial. Hence the possible advantage of a vegetarian diet.

Weight reduction

There is no doubt from population studies that there is a close relationship between blood pressure and body mass index even after allowance for the tendency to overestimate blood pressure in obese people. Patients with high blood pressure who are obese do sustain a fall in pressure when they reduce weight (see Figure 10.4).[11]

Studies of change in weight in relation to changes in blood pressure suggest that an eleven pound (five kilogram) fall in body weight is associated with a 5 mmHg fall in systolic blood pressure. This implies that many obese people with mild hypertension can normalize their blood pressure if they reduce weight, but that weight reduction alone is unlikely to be sufficient to normalize pressure in people with diastolic pressures above 110 mmHg. Some studies have reported that this fall in pressure is independent of the reduction in sodium intake that occurs with dieting.

It is important to encourage patients who are obese to try to reduce weight. This may be difficult to achieve and there is little point in encouraging patients with crash diets which result in dramatic falls in weight if, as soon as a normal diet is resumed, weight rises again. It is much

Figure 10.3 *(left)* Typical meal high in salt and fat, and *(right)* foods which should be encouraged in the diet. The meal on the right contains approximately twenty times less saturated fat and salt.

better to try to get patients used to eating less food over a longer period of time. A two pound (one kilogram) weight loss per week is all that should be aimed for, but the patient should be encouraged to carry on with this over many months. There is some evidence that professional dietitians are better than doctors at persuading their patients to lose weight.

Alcohol

There has recently been an increased awareness of the relationship between high alcohol intake and hypertension. Some of the epidemiological evidence is discussed in Chapter 3. Hypertensive patients have a higher frequency of alcohol abuse than normotensives. It is important to note that when alcoholics or heavy drinkers stop drinking, their blood pressures fall fairly rapidly.

While most mortality studies have shown an inverse relationship between alcohol intake and coronary heart disease, drinkers having lower cholesterol levels and less heart disease, they do show a strong positive relationship between alcohol and stroke. This relationship may be due to alcohol-induced hypertension, but it is also possible that acute strokes

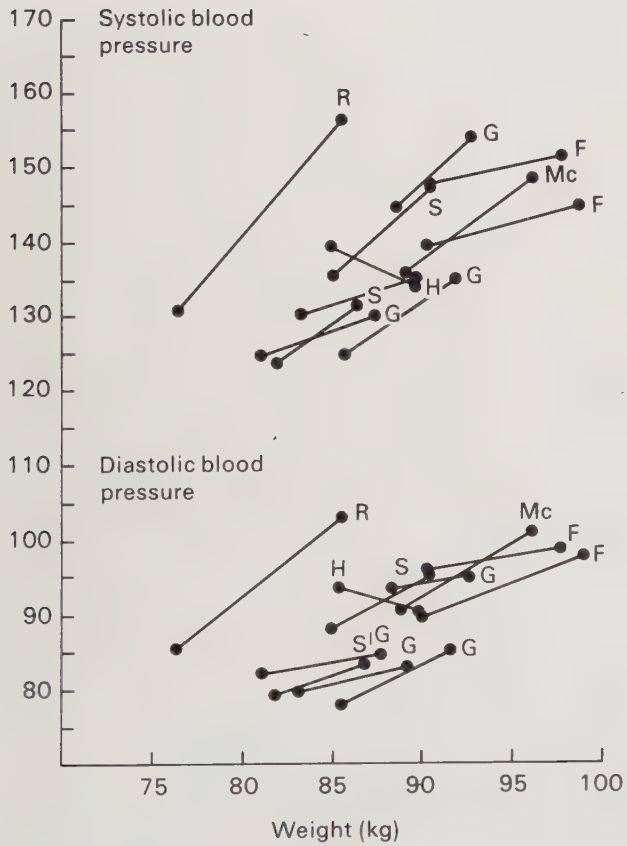

Figure 10.4 Published studies on the effect of weight reduction on blood pressure. Each line represents one study.

may occur after binge drinking, due to direct intracerebral vasoconstriction.

The mechanism of the relationship between alcohol intake and blood pressure is unknown.[12] But given in moderate quantities alcohol has multiple biochemical effects, on renin, aldosterone, cortisol, catecholamines, vasopressin and water output. One interesting phenomenon is that moderate drinkers who consume the equivalent of around seven pints (three litres) of beer per week (or the equivalent of 140 g of alcohol) have lower pressures than teetotallers. Above this level, however, there is a close relationship between alcohol consumption and the height of blood pressure. This is found in both beer drinkers and spirit drinkers.

Alcoholic patients may develop very high blood pressures while they are withdrawing from alcohol, and this pressor

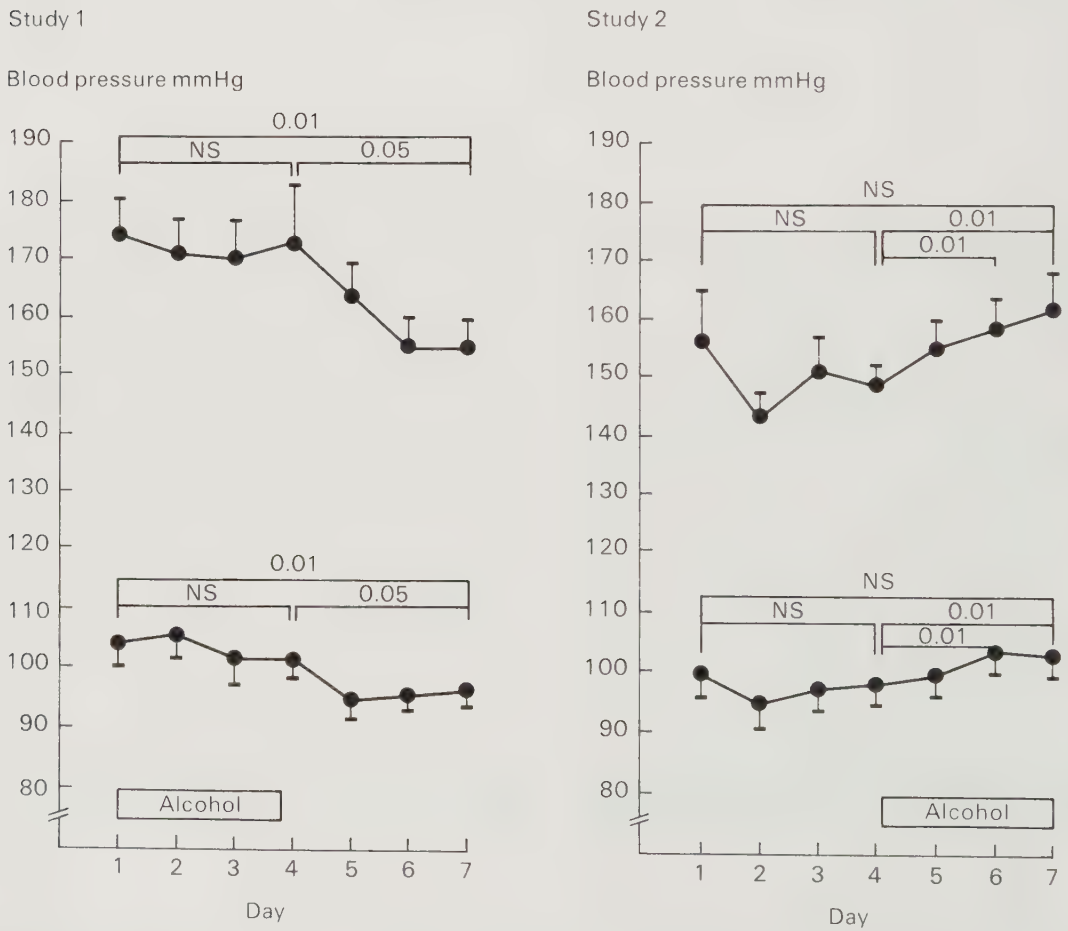

Figure 10.5 The effect on blood pressure of stopping and restarting drinking alcohol.[12]

response may be mediated by catecholamine release.[12] This mechanism probably does not explain the relationship between hypertension and more modest intake in non-alcoholics. However, hypertensive patients do have higher liver enzyme (gamma glutamyl transpeptidase) levels than normotensives. Even hypertensives who drink moderately sustain a fall in blood pressure when they stop taking alcohol (see Figure 10.5).

Alcohol intake is notoriously difficult to measure in both clinical and epidemiological practice. Detailed questionnaires are available, with separate questions about the consumption of beers, spirits and wines but answers cannot always be assumed to be reliable. Biochemical markers of high alcohol intake are a rasied mean red-cell volume (MCV) and raised GGT. Alcoholics and even people who simply consume a lot of alcohol also tend to have hyperuricaemia. Rib fractures on chest x-ray also suggest a high alcohol intake.

In both normal subjects and hypertensive patients, the rapid intake of about three pints (1.5 litres) of beer raises blood pressure, whereas the same quantity of alcohol-free beer has no effect.

In clinical practice, therefore, the following points are worth considering:

1. Clinical evidence of high alcohol intake should be looked for in hypertensive patients. Plethora and a Cushingoid appearance are two important clinical markers (see Chapter 7).
2. All patients should be screened with estimations of MCV (in the full blood count) and of liver enzymes, particularly gamma glutamyl transferase.
3. Patients who consume more than seven pints (three litres) of beer per week should be advised to reduce their intake.
4. Patients can be advised that it is safe to consume some alcohol, but that they should not exceed seven pints (three litres) of beer, or a half bottle of spirits or three bottles of wine per week (see Table 10.3).

MEN	WOMEN
14 pints of beer	7 pints of beer
28 glasses of wine	14 glasses of wine
28 glasses of sherry	14 glasses of sherry
28 small glasses of spirits	14 small glasses of spirits

Permitted tobacco intake: Nil

Table 10.3 Absolute maximum weekly consumption of alcohol for hypertensive patients.

Smoking

This is an independent risk factor for the premature development of arterial disease and particularly for heart attacks and sudden death. There is overwhelming evidence now that stopping smoking is of immense benefit. Indeed, a study of British general practitioners showed that after three months of stopping smoking the risk of a heart attack was reduced to about the same level as for non-smoking doctors.

The mechanism whereby smoking may cause an increased risk of arterial disease is controversial. It could be partly due to a direct effect of nicotine causing increased

excitability of the heart and arrhythmias, or to a high level of carbon monoxide in the blood making the development of atheroma more likely.

Smoking is, after high blood pressure, the most preventable cause of death in the Western world. It is estimated that in the UK alone, over 200,000 persons per year die from smoking. Many people who are being treated for mild hypertension have not even been told to stop smoking. The risk in these patients from smoking is greater than the risks from their mild hypertension.

Smoking a cigarette causes an acute rise in blood pressure. Confusingly, however, epidemiological evidence suggests a slight negative effect on blood pressure, i.e., smokers have slightly lower blood pressures than non-smokers (see Chapter 3). The only exception to this negative smoking/blood pressure relationship is the strong positive association between cigarette smoking and the malignant phase of hypertension.

All patients who smoke should be told to stop. The risks of high blood pressure and of smoking in the same individual are not only additive but synergistic, i.e., the risk is greater than for the two factors added together. A careful explanation of this synergism may produce a far greater willingness in the patient to give up smoking.

Caffeine

Coffee drinking has been demonstrated to cause an acute rise in blood pressure. Epidemiological evidence does not, however, show any relationship between caffeine consumption and blood pressure and cutting back on coffee intake does not cause a fall in blood pressure. People who drink a lot of coffee may also smoke or drink heavily, and this does influence their cardiovascular risk.

RELAXATION

The most effective way of lowering blood pressure is to sleep. Indeed, if we spent the whole of our life asleep, very few of us would have high blood pressure. This fall in blood pressure during sleep is largely due to relaxation of the voluntary muscles. The reflex can be clearly demonstrated by relaxation of all muscles followed by measurement of the blood pressure. The thumb is then opposed against the index finger in isometric contraction. There will be a marked increase in diastolic pressure of approximately 10 to 20 mmHg.

All the relaxation therapies, for example, biofeedback, transcendental meditation, yoga, sleep therapy, behaviour therapy and psychotherapy use this simple but basic physiological reflex. There has been one well conducted randomized study which did show a fall in blood pressure of both nomotensives and hypertensives after relaxation therapy.[13] More studies are needed to confirm this.

It is sensible to review the lifestyle of patients with hypertension and ensure that they are not subjecting themselves to unnecessary stress, though there is little point in forcing people to relax who do not want to. Evangelists for fringe remedies should be treated with suspicion.

EXERCISE

During dynamic exercise such as running, swimming or bicycling systolic pressure rises, diastolic pressure falls and heart rate increases. In physically fit people, the rise in systolic pressure and heart rate are less and blood pressures may fall to lower levels after exercise. However, most positive studies claiming a relationship between blood pressure and exercise have not taken into account other alterations of lifestyle in fit people, including changes

in diet, reduction of alcohol consumption and stopping smoking.

People who are fit feel better. This in itself is sufficient reason for encouraging patients to take plenty of exercise, but adequate warnings must be given. Sudden strenuous exertion may be harmful, particularly in unfit patients. Isometric exercise, unlike dynamic exercise, causes a significant rise in both diastolic and systolic pressures, and could be dangerous in hypertensive patients. Carrying heavy suitcases may precipitate angina in patients with ischaemic heart disease and could precipitate cerebral haemorrhage in those with uncontrolled blood pressure.

REST

Putting patients to bed in hospital will have a marked blood pressure lowering effect, partly because of relaxation of voluntary muscles but also because there is a loss of sodium and water with decreased physical activity. There is no evidence that bedrest or admitting patients to hospital has any longterm effect on blood pressure. Patients with very severe or resistant hypertension may be admitted pending investigation and initiation of complex drug regimes. There is, however, not much point in controlling blood pressure only in hospital when patients' blood pressures usually rise and become uncontrolled when they are discharged.

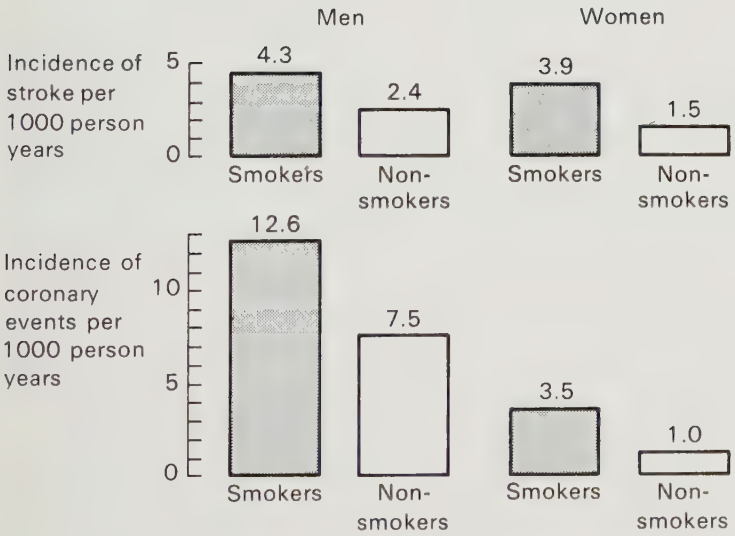

Figure 10.6 Incidence of stroke and coronary events in mild hypertensives who were smokers or non-smokers and who received placebo therapy in the MRC trial of mild hypertension (from MRC Trial Report, *Brit. Med. J. 291*, 1985, 97–104).

PRACTICAL POINTS

- All patients with high blood pressure, whether they are receiving anti-hypertensive drugs or not, should receive the following advice:

  1. Eat a more healthy diet
     —less salt
     —more fresh fruit and vegetables
     —less saturated fat and substitute with polyunsaturated fat
     —avoid being overweight
  2. Drink no more than one pint of beer (0.5 litre) or its equivalent per day
  3. Stop smoking.

- These forms of non-drug therapy can be effective in lowering blood pressure and are additive to drug treatment.

- They may prevent the progression of mild hypertension to more severe levels.

- Only with careful explanation and reinforcement will patients stick to their doctor's advice.

- Perhaps the best person to reinforce this advice is the clinic or practice nurse.

- The nursing profession has an increasing role to play, not only in the detection of hypertension, but also in its management. In particular nurses should be specially trained in the non-pharmacological treatment of high blood pressure.

- These measures would probably usefully be adopted by the whole population.

11
A review of antihypertensive drugs

BACKGROUND

In general, over the last thirty years drugs for lowering blood pressure have become more effective and, more important, they now have fewer side-effects. The improvement is likely to continue, and raises the questions of and when which new drug should be used. The best criterion is whether the new drug reduces the chances of stroke and heart attacks in addition to the blood pressure. In practice, we rarely know this. The choice therefore depends on:

- The experience of the doctor with a particular drug
- Its effectiveness in lowering blood pressure
- Side-effects
- Cost.

Ideally, each patient should undergo some sort of assessment to decide which of the appropriate drugs is the most tolerable and effective in his or her case. After all, the patient may receive this treatment for the rest of his or her life. Many drugs, while not having the serious side-effects of the older agents, have more subtle effects which may reduce the quality of life on a longer term basis. It is usually found that a combination of low doses of drugs has an additive effect on blood pressure, with fewer side-effects than high doses of one agent.

This chapter discusses the many drugs that are available, their mechanisms and their side-effects. In addition, information is provided on the current view of their role in the management of hypertensive patients (see Table 11.1).

Diuretics
Beta adrenoceptor blockers
Calcium-entry antagonists
Angiotensin-converting enzyme inhibitors
Others
Alpha adrenoceptor blockers
Peripheral vasodilators
Central acting agents
Adrenergic neurone blockers

Table 11.1 Drugs that lower blood pressure.

DIURETICS

Thirty years after their introduction, there is increasing concern about potentially harmful metabolic effects of diuretics and speculation that they may possibly cause arrhythmias in some patients. In men, impotence has also emerged as a problem. Diuretics are additive to nearly all of the blood pressure lowering drugs, particularly the beta-blockers and converting-enzyme inhibitors. Many of the arterial vasodilators like hydralazine and minox-

idil cause sodium retention which may offset their the blood pressure lowering effect. In this situation diuretics must be used, and some patients may become oedematous without them.

Prostaglandin-inhibiting drugs, particularly indomethacin, may interfere with the effects of diuretics, and when introduced in a previously well-controlled patient may cause an unexpected rise in blood pressure.

Thiazide diuretics

There are slight differences in the duration of action and major differences in dosage between the different thiazides but they can all be given once daily. Related sulphonamide compounds such as chlorthalidone and metolazone are longer acting and more powerful.

All the thiazide diuretics have a fairly flat dose–response curve, so that increasing the dose has little further effect on blood pressure but does increase the metabolic consequences on potassium, glucose, lipids and uric acid.[1] It is best to use the minimum dose necessary, as nothing is gained by giving larger doses.

	Normal daily dose for hypertension
Thiazides	
*Bendrofluazide	2.5 mg
*Hydrochlorothiazide	12.5 to 25 mg
Cyclopenthiazide	0.25 mg
Chlorothiazide	500 mg
Hydroflumethiazide	50 mg
Thiazide related compounds	
Chlorthalidone	12.5–25 mg
Indapamide	2.5 mg
Mefruside	25 mg
Xipamide	20 mg
Metolazone	5 mg
Polythiazide	1 mg
Loop diuretics	
Frusemide	40 mg (more in renal failure)
Bumetanide	1 mg (more in renal failure)
Piretanide	6 mg
Potassium sparing diuretics	
Amiloride	5–10 mg
Triamterene	50 mg
Spironolactone	25–100 mg
*Recommended for routine treatment	

Table 11.2 Dosage for diuretics.

Mode of action The thiazide diuretics act on the renal tubules to block sodium and chloride reabsorption. After a degree of sodium and water loss has occurred, compensatory mechanisms block the effect on the kidney so that within a few days no additional loss of sodium occurs but total body sodium is maintained at a slightly lower level as long as the diuretic is taken. This causes a fall in the extracellular fluid volume and a small decrease in plasma and blood volume. With the loss of sodium and water there is a rise in renin release from the kidney leading to the formation of the powerful vasoconstrictor angiotensin II. The fall in blood pressure with a diuretic is largely determined by the fall in extracellular volume and the compensatory rise in angiotensin II levels. This may explain why diuretics are more effective in black patients and in older white hypertensive patients, both of whom tend to have lower plasma renin levels and a smaller rise in plasma angiotensin II with diuretic therapy.

Beta-blockers partially inhibit the renin release caused by diuretics, and the converting-enzyme inhibitors enalapril and captopril almost totally abolish the compensatory rise in plasma angiotensin II levels. For this reason beta-blockers or converting-enzyme inhibitors are very effective when used in combination with

diuretics. However, there is a flat dose response to diuretics in the presence of a beta-blocker, whereas with the converting-enzyme inhibitors increasing the dose of diuretic does cause a further fall in blood pressure.

Side-effects Thiazide diuretics are well tolerated, particularly at lower doses. Very rarely, severe reactions do occur causing skin rashes, thrombocytopenia and leucopenia. There was therefore some surprise when the MRC Trial on Mild Hypertension, using large doses of bendrofluazide (10 mg daily) reported a higher incidence of impotence with thiazides compared with beta-blocker or placebo therapy (see Figure 11.1). Whether this adverse effect occurs at lower doses of thiazides remains to be seen. Nevertheless, patients on thiazides should be questioned about this as it may be an important but previously unrecognized problem.

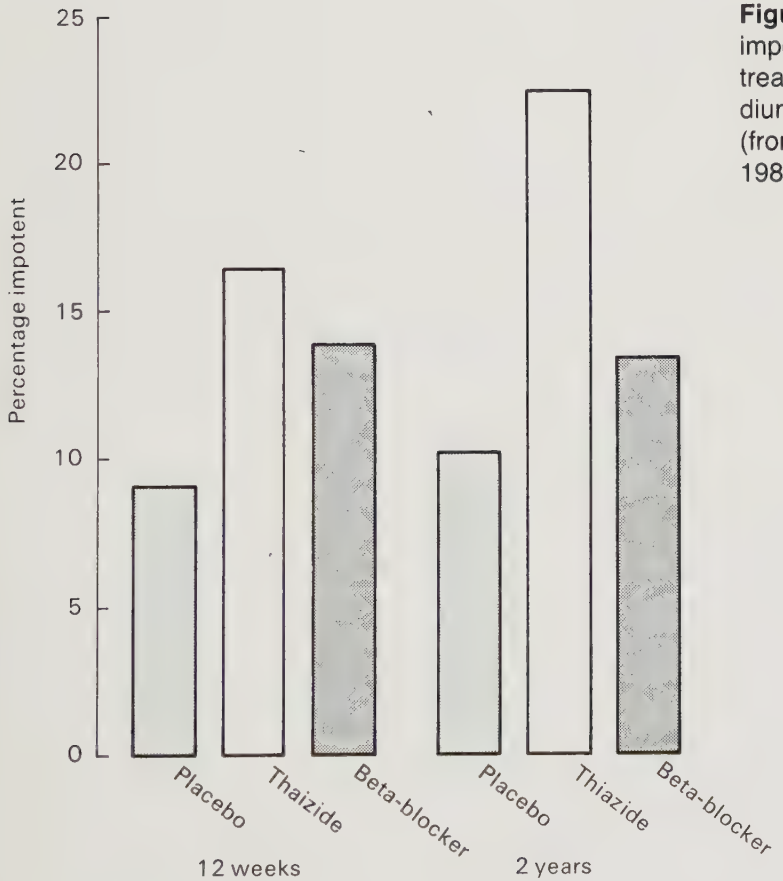

Figure 11.1 Frequency of impotence in 1130 men treated with placebo, thiazide diuretics or beta-blockers (from MRC Trial, *Lancet 2*, 1981, 539–43).

The metabolic problems of thiazide diuretics

Hypokalaemia Almost all patients treated with a thiazide sustain a fall in plasma potassium. This fall varies with the dose but averages between 0.3 and 1.0 mmol/l. A high salt diet increases the fall in plasma potassium, whereas in those patients who restrict their salt intake the fall is smaller. The dangers of hypokalaemia are many. The MRC trial demonstrated that in patients receiving 10 mg of bendrofluazide daily there was a higher incidence of multifocal ventricular ectopic beats in thiazide-treated patients compared with those receiving either a beta-blocker or placebo therapy.[2] This effect may be increased by exercise (see Figure 11.2). There is also evidence that patients who have suffered a heart attack have a worse prognosis if they have a low plasma potassium. As hypertensives are especially prone to heart attacks, and the commonest cause of hypokalaemia is diuretic therapy, this finding is worrying although the MRC trial demonstrated no excess mortality in the thiazide-alone group.

The plasma potassium level should be measured in all patients before starting diuretic therapy. If it is already low further tests should be instituted. After a few months of treatment it is worth rechecking plasma levels, but there is some doubt as to whether the fall in plasma potassium is accompanied by a fall in total body potassium. It is possible that it is due to redistribution rather than loss

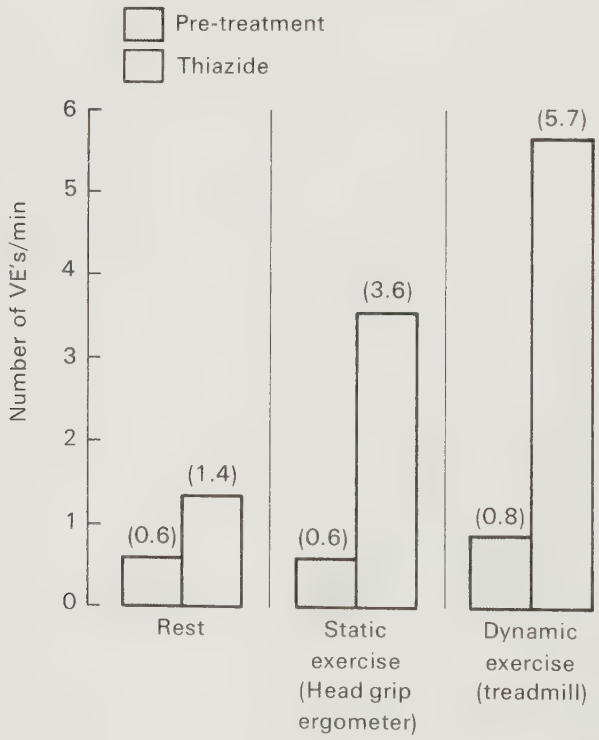

Figure 11.2 The frequency of ventricular ectopic beats in patients on thiazide diuretics (from J. W. Hollifield, *RSM International Congress Series 44*, 1981).

of potassium from the body. In general, clinicians have neglected to watch plasma potassium levels. This is because hypokalaemia rarely causes obvious clinical side-effects. It is the longterm effects that are worrying, and this is one of the main reasons why beta-blockers are preferred as the first-line antihypertensive agents.

Potassium supplements should be used only when plasma potassium falls to below 3.5 mmol/l, or if there is concurrent heart failure. Potassium supplements themselves have side-effects and are not always effective and are therefore only rarely indicated. Most of the combined diuretic and potassium chloride tablets contain trivial amounts of potassium and are of no benefit.

Small doses of thiazides (for example, bendrofluazide 2.5 mg daily or hydrochlorothiazide 12.5-25 mg daily) cause a smaller fall in plasma potassium and when combined with beta-blockers usually cause no fall. This is because beta-blockers themselves cause a slight rise in plasma potassium by virtue of their suppression of renin and aldosterone levels. This also occurs with ACE inhibitors.

Profound hypokalaemia If serum potassium falls to very low levels, the possibility of another underlying cause of hypokalaemia—particularly primary aldosteronism—should be considered.

Hyperuricaemia All of the thiazide diuretics cause an increase in plasma uric acid levels and may occasionally precipitate acute gout. It is uncertain whether a symptomless longterm rise in serum uric acid level is important. Hyperuricaemia is common in hypertensive patients even without thiazides, but it is doubtful whether serum uric acid is an independent cardiovascular risk factor. Lower doses of diuretics have less effect on uric acid levels.

Glucose tolerance Many patients treated with thiazide diuretics on a longterm basis develop a deterioration in glucose tolerance (see Figure 11.3). Some develop elevated fasting blood glucose levels and, more rarely, frank diabetes may be precipitated. In patients who already have diabetes there may be a slight worsening of diabetic control. Thiazides should not

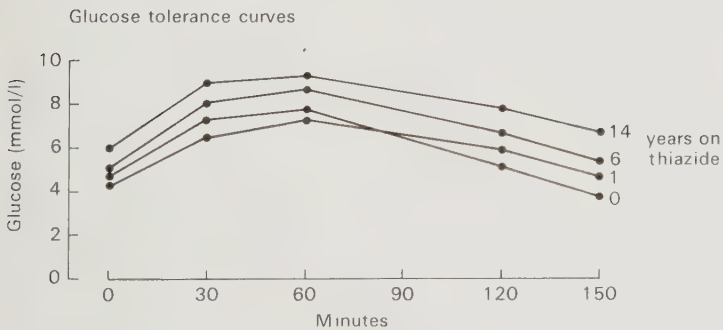

Figure 11.3 The longterm effect of thiazide diuretics on glucose tolerance (from M. B. Murphy, *Lancet 2*, 1982, 1293–5).

therefore be used in people who have borderline glucose intolerance. It is not uncommon in the diabetic clinic to see patients who can normalize their blood glucose levels simply by changing from a thiazide diuretic to another agent.

Blood lipids There is general agreement that a small rise in plasma cholesterol and triglyceride levels results from longterm treatment with thiazide diuretics. This may hasten the development of vascular disease and partly offset the benefits of reducing the blood pressure.

Calcium Thiazides sometimes elevate plasma calcium levels to the range where a diagnosis of hyperparathyroidism should be considered.

Other problems In those patients who are already salt depleted, diuretics may cause further volume depletion. Patients with chronic renal disease may show a deterioration in renal function. Rarely thiazides cause large falls in plasma sodium with frank hyponatraemia (serum sodium 110 to 125 mmol/l). Usually there is some intercurrent illness, but the hyponatraemia may cause confusion, dehydration, vomiting and muscle weakness.

A small rise in packed cell volume and haemoglobin level is common with diuretics. Both are potential risk factors for strokes. Thiazides also increase platelet aggregation, which may cause thrombotic disease.

Pregnancy Thiazides should not be used for hypertension in pregnancy as they may reduce placental bloodflow (see Chapter 16).

Loop diuretics

Frusemide and bumetanide act on the ascending limb of the loop of Henle and block sodium reabsorption. They are much faster-acting diuretics than the thiazides, with a shorter duration of action. They have not therefore been widely used in the first-line treatment of hypertension, neither is this use advised. They are used in resistant hypertension, in combination with other drugs, and also in patients with renal impairment where high doses may be necessary. The loop diuretics have the same sort of complications as the thiazides although frusemide at low doses may cause fewer effects. They are useful in patients receiving vasodilators who develop fluid retention, and they are almost always needed when minoxidil is used in very resistant hypertension. They are also useful in combination with ACE inhibitors. Slow-release forms of frusemide and bumetanide are now becoming available and may be useful.

Potassium-sparing diuretics

These drugs act on the distal renal tubule and reduce potassium excretion at the same time as increasing sodium and water loss. There are three potassium-sparing diuretics currently available: spironolactone, triamterene and amiloride.

Spironolactone is an aldosterone antagonist which may also have a direct effect on the distal renal tubule. Given alone in large doses it can control the blood pressure in patients with primary aldosteronism prior to surgery, or in cases where surgery is contraindicated. It is as effective as a thiazide diuretic, although it has a slower onset of action. It has fewer metabolic consequences than the thiazides but may cause a slight elevation in plasma potassium. Patients with renal failure should not therefore be given spironolactone unless plasma potassium is carefully

monitored, as dangerous hyperkalaemia may result.

Spironolactone unfortunately has endocrine side-effects including gynaecomastia and loss of libido in men, and intermenstrual bleeding in premenopausal women.

Combined with other diuretics it is useful in preventing a fall in plasma potassium. Spironolactone is also marketed combined with a thiazide diuretic but these preparations usually contain an unnecessarily large amount of thiazide and are therefore not recommended.

Triamterene This drug is less effective in lowering blood pressure than spironolactone but it does partially block the potassium lowering effect of thiazide diuretics. It has therefore been combined with thiazide diuretics to prevent the fall in plasma potassium.

Amiloride Although structurally different to triamterene, amiloride has a similar action on the distal tubule. It has therefore been marketed combined with a thiazide diuretic. This combined preparation can cause hypokalaemia, and, rarely, profound hyponatraemia.

Both triamterene and amiloride have been reported to cause nausea, flatulence and skin rashes. Both drugs, like spironolactone, can cause hyperkalaemia in patients with renal failure.

Indapamide

This diuretic is similar to the thiazides but it is claimed to have additional blood pressure lowering effects independent of the loss of sodium.

BETA-BLOCKERS[3]

Potentially beta-blockers have advantages independent of their blood pressure lowering effect; they may also reduce the incidence of coronary disease. However, recent trials in hypertension have shown only a marginal effect in non-smokers and no effect at all in smokers.

Mode of action

The beta-blockers compete with the endogenous catecholamines for adrenergic beta-receptors. Beta-receptors can be divided into two classes: beta-1 and beta-2 receptors. Blocking the beta-1 receptors reduces the heart rate and the contractility of the heart with a concomitant reduction in cardiac output. This may be part of the mechanism of the blood pressure lowering effect. Blockade of the beta-2 receptors causes vasodilatation in voluntary muscle but can cause bronchoconstriction, particularly in asthmatic subjects.

Beta-blockers inhibit renin release, leading to falls in plasma angiotensin II levels which may explain some of the blood pressure lowering action. Beta-blockers are less effective in patients with low plasma renin levels, particularly in blacks and older white hypertensives.

Classification

All beta-blockers are effective in reducing blood pressure. There are, though, some important differences between them, which are shown in Figure 11.4.

Cardioselectivity Some beta-blockers are not cardioselective (for example, propranolol and oxprenolol) as they block both beta-1 and beta-2 receptors equally. The cardioselective beta-blockers (acebutolol, atenolol, metoprolol) have a greater effect on cardiac beta-1 receptors. There is no difference in the blood pressure lowering effect of selective and nonselective beta-blockers.

Intrinsic sympathomimetic activity Like many competitive inhibitors, some beta-blockers stimulate the beta-receptors as well as block them, particularly when endogenous levels of catecholamines are low. This intrinsic sympathomimetic activity (ISA) or partial agonist activity (PAA) is seen particularly with pindolol, oxprenolol and, to a lesser extent, acebutolol.

Membrane-stabilizing activity Some beta-blockers also have a quinidine-like membrane-stabilizing effect (for example, propranolol) but this is not of any clinical significance.

Lipophilicity Some beta-blockers are more lipid-soluble that others. Lipid-soluble (lipophilic) drugs are more likely to enter the brain and cause central side-effects. The less lipid-soluble (more hydrophilic) drugs such as atenolol, acebutolol, sotalol and nadolol may cause fewer central effects.

Lipid-soluble drugs are mainly metabolized by the liver, and water-soluble agents are excreted by the kidney. This is significant if there is either hepatic or renal impairment, and may influence the choice of beta-blocker.

Duration of action All beta-blockers reduce blood pressure by about the same amount. This response starts within one to two hours of a single oral dose. Most beta-blockers can be given once a day.

There are wide variations in the total daily dose of each individual drug. It is probable that in many patients lower doses are needed than those recommended by the manufacturers (see Table 11.3).

Side-effects of beta-blockers (Table 11.4)

Heart failure When these drugs were first introduced there was some concern that they might precipitate heart failure, particularly in patients with angina who may already have damaged heart muscle. In patients with high blood pressure where the left ventricle is performing well beta-blockers are unlikely to precipitate heart failure. Nevertheless, patients with high blood pressure and heart failure should not be given beta-blockers except under very carefully supervised conditions (see Chapter 14).

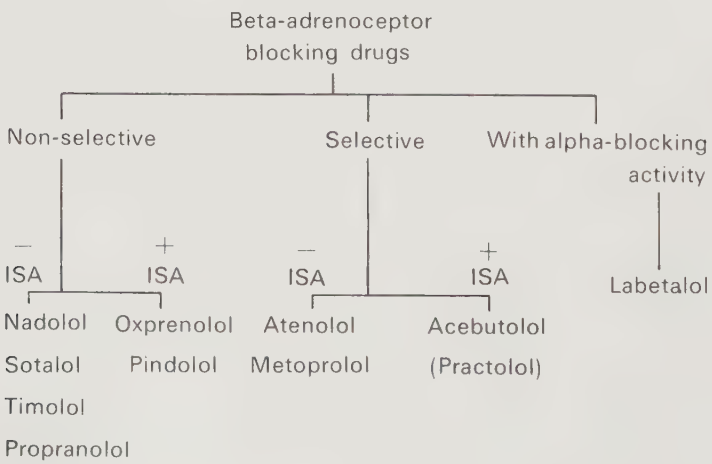

Figure 11.4 A classification of beta-adrenoceptor blockers based on cardioselectivity and intrinsic sympathomimetic activity.

Reduction in peripheral bloodflow Because of the reduction in cardiac output and a reflex increase in peripheral resistance, all beta-blockers tend to reduce peripheral bloodflow and cause cold hands and feet, particularly in colder climates. They may worsen symptoms in patients with Raynaud's disease or intermittent claudication. If symptoms are mild advice about keeping hands warm and wearing gloves may suffice, particularly if the clinician does not want to alter the antihypertensive regime. In severe peripheral vascular disease, gangrene has been precipitated by the use of beta-blockers. It is possible that beta-blockers with partial agonist activity, for example, pindolol and oxprenolol, are less likely to do this, but beta-blockers are best avoided and calcium-entry antagonists or converting-enzyme inhibitors should be used instead.

Bronchospasm All beta-blockers may precipitate bronchospasm, especially if there is a preceding history of asthma. The more cardioselective beta-blockers atenolol, metoprolol and acebutolol are less likely to have this effect. They are still contraindicated in asthmatics, although they may be safer in patients with chronic obstructive airways disease. If there is any possibility of precipitating bronchospasm with beta-blockers it is probably better to use other types of antihypertensive drugs.

Reduction in exercise tolerance All beta-blockers cause a reduction in exercise tolerance and this can be a major problem for active young patients who notice, for example, that they feel tired when climbing stairs, particularly with a feeling of heaviness in the legs. Either a calcium-entry antagonist or a converting-enzyme inhibitor should be used instead.

Cardioselective blockers	
Atenolol	25 – 100 mg
Metoprolol	50 – 400 mg
Acebutolol	200 mg – 800 mg
Non-selective beta-blockers	
Propranolol	80 – 360 mg
Betaxolol	10 – 40 mg
Nadolol	20 – 80 mg
Penbutolol	(available only in combined preparations)
Sotalol	80 – 160 mg
Timolol	5 – 10 mg
Beta-blockers with partial agonist activity	
Oxprenolol	80 – 320 mg
Pindolol	5 – 15 mg

Table 11.3 Dosage for beta-adrenoceptor blockers.

Sleep disturbance	Heart failure
Nightmares	Reduction of exercise tolerance
Lethargy	Raynaud's syndrome
Bronchospasm	Claudication
Bradycardia	
Impotence	

Table 11.4 Some side-effects of beta-blockers.

Central nervous problems Beta-blockers may cause sleep disturbance, vivid dreams and nightmares. These may be more common with the lipid-soluble beta-blockers such as propranolol and oxprenolol. The hydrophilic blockers atenolol, nadolol or sotalol should be tried, but if sleep disturbance persists a calcium-entry antagonist or converting-enzyme inhibitor should be used instead. More commonly beta-blockers may cause a subtle loss of intellectual function or drive, or energy, and if this occurs other forms of therapy should be considered.

Diabetes mellitus Theoretically, beta-blockers could interfere with insulin secretion. More importantly, they may interfere with the symptoms and metabolic responses to hypoglycaemia, in insulin-dependent diabetics, although this may be less likely with the cardioselective beta-blockers. Diabetics should nevertheless be warned that the symptoms of hypoglycaemia may be masked by the therapy they are taking. Beta-blockers are probably best avoided in very brittle diabetics on insulin, but in most other cases they can be used with safety.

CALCIUM-ENTRY ANTAGONISTS

These were known to lower blood pressure some years ago, but this potential was not exploited until the 1980s. They are very effective blood pressure lowering agents in all grades of hypertension. However, their exact mode of action on the arteriolar smooth muscle cell has yet to be elucidated. It is thought that they reduce the concentration of free ionized calcium within the cell, thereby relaxing smooth muscle and causing arteriolar vasodilatation. Indeed, it has been suggested that this class of compounds may at least in part be attacking the mechanism whereby blood pressure is raised. In view of their effectiveness in lowering blood pressure large numbers of calcium-entry antagonists are now being developed, although they may not differ from each other significantly. All are vasodilators, but some, such as verapamil, have a greater negative ionotropic and chronotropic effect on the heart. Their major advantage is that unlike the older vasodilators they do not cause tachycardia or fluid retention.

Verapamil, nifedipine and diltiazem have been shown, at least acutely, to be natriuretic, and probably chronically they have a mild diuretic action, which may further reduce blood pressure. Most patients notice that they can exercise normally whilst receiving calcium-entry antagonists and there is no interference with cerebral function.

Verapamil[4]

Verapamil was originally introduced in the 1960s as a beta-blocker and used intravenously as an anti-arrhythmic agent, but it was subsequently realized to be a calcium-entry antagonist. When used in

	Normal daily dose
Nifedipine	10 to 40 mg twice daily
Verapamil	160 – 320 mg twice daily
Sustained release preparation	240 mg once daily
Diltiazem	60 – 120 mg twice daily
Nicardipine	20 – 30 mg three times daily

Table 11.5 Dosage for calcium-entry antagonists.

patients already receiving a beta-blocker it may rarely cause sinus arrest. In view of this, there has been a reluctance to combine oral verapamil with a beta-blocker.

On its own verapamil has been shown to be an effective blood pressure lowering drug.

Dosage Verapamil is usually started at 80 mg twice daily and can be built up to 160 mg twice daily, with increased effect. A once-daily 240 mg tablet has recently become available

Side-effects Its major side-effect is constipation, which occurs particularly with higher doses. It can cause facial flushing and redness of the hands and feet. In most patients, however, it is well tolerated.

Nifedipine[5]

Like verapamil, nifedipine is a calcium-entry antagonist which was initially used in the treatment of angina pectoris. It has less effect on cardiac conduction, and possibly a greater peripheral vasodilating effect.

Dosage The 10 mg capsules are very rapidly absorbed. Recently, 10 and 20 mg tablets of nifedipine have been developed, which are less rapidly absorbed and are slightly longer-acting than the capsules, so in longterm therapy these should be used in preference to the capsules.

The 10 and 20 mg tablets of nifedipine can be given twice daily. There is good evidence of an increasing dose response, and 40 to 60 mg twice daily may be prescribed safely. Blood pressure falls within one to two hours of the first dose being taken. For this reason, nifedipine tablets are very useful when managing severe or malignant hypertension.

Side-effects Nifedipine commonly causes facial flushing and tingling of the extremities, and a sensation of warm hands and feet and occasionally headaches. These symptoms usually occur with the first dose, particularly with the 10 mg capsules, and are less frequent with the 20 mg tablets.

A few patients develop oedema of the legs. This occurs particularly in middle-aged women. Unlike the direct arteriolar vasodilators, it seems that this is not

1 Nifedipine and nicardipine	**2 Verapamil**
(a) Facial flushing	(a) Constipation
(b) Headaches	(b) Facial flushing
(c) Ankle oedema	(c) Nausea
(d) Lethargy	(d) Vomiting
(e) Gum hyperplasia	(e) Brady-arrhythmias (when used with beta-blockers)
(f) Nocturia	

Table 11.6 Side-effects of calcium-entry antagonists.

related to renal sodium and water retention but may be due to local tissue factors encouraging the formation of oedema. This side-effect is sometimes abolished by reduction of the total daily dose. Altogether about 10 to 15 per cent of patients are unable to tolerate nifedipine, but the remainder encounter no problems.

Indications for nifedipine Nifedipine has been given in severe hypertension resistant to other therapy and has been found effective. It is additive to a beta-blocker but there is some controversy as to whether diuretics are additive to it. Recent reports have shown that the converting-enzyme inhibitor captopril is additive to nifedipine and this can be an effective combination in very resistant hypertension. As nifedipine has been widely used in angina for many years without any longterm adverse effects, it is likely that the same will apply to hypertension. It is particularly useful in patients where there is a contraindication to beta-blockers or there are side-effects. Nifedipine has probably replaced hydralazine as the most effective third-line agent in resistant hypertension, and is now being increasingly used as a first-line agent (see also Chapter 12).

Nicardipine

This newer calcium blocker has virtually no cardiac side-effects.

Diltiazem[6]

This calcium-entry antagonist has similar vasodilating properties to nifedipine and fewer chronotropic and inotropic effects than verapamil. It is used fairly widely in the USA but little-known in the UK.

Many more calcium-entry antagonists will become available over the next few years but it remains to be seen whether they will have any special advantages.

ANGIOTENSIN CONVERTING-ENZYME INHIBITORS (ACE INHIBITORS)[7]

These drugs were designed to block the enzyme that is responsible for converting angiotensin I to angiotensin II. The first inhibitor was found in snake venom, and from this an injectable peptide was developed. Subsequently compounds that could be taken orally were synthesized. Captopril, the first of this class of compounds, was originally introduced for resistant hypertension but has been found to be effective in mild to moderate essential hypertension as well. More recently enalapril has become available and it is likely that there will soon be several more ACE inhibitors on the market.

ACE inhibitors also prevent the breakdown of bradykinin to inactive kinins, thus increasing circulating levels of this vasodilator hormone, and they influence prostaglandin metabolism. It is uncertain whether these biochemical effects also contribute to the antihypertensive response.

Captopril

This is rapidly absorbed and starts to lower blood pressure within about fifteen to thirty minutes of the first dose. Two hours after a single oral dose, there is virtually no circulating angiotensin II present. The drug is partially metabolized by the liver and is excreted in the urine along with its metabolites. Therefore, both may accumulate in renal failure.

Captopril causes a fall in blood pressure, dependent on the initial plasma level of angiotensin II. Patients with very high levels of angiotensin II, as may be seen in malignant hypertension or renal artery stenosis, may sustain a larger fall in pressure. Care should also be taken when giving captopril or enalapril to patients already on large doses of diuretics. Patients with low levels of renin have a smaller

response. In them, almost invariably, a diuretic has to be added which raises plasma renin levels and removes some fluid, thus rendering the ACE inhibitors more effective.

Dosage In most patients, captopril is started on a dose of 12.5 to 25 mg twice daily. The total daily dose should never exceed 100 mg. In severe renal failure as little as 6.25 mg twice daily may control the blood pressure.

Side-effects Patients often volunteer that they feel remarkably well on captopril. Indeed, a recent double-blind study has confirmed that captopril has fewer side-effects and less effect on the quality of life than propanolol or methyldopa.[8] Because the drug is acting peripherally it does not interfere with intellectual function or cause drowsiness or deterioration in exercise tolerance. Although the drug was well tolerated in the original trials, where it was given in large doses, particularly to people with renal failure, occasional serious side-effects (proteinuria and leucopenia) were encountered. When captopril is used in lower doses (12.5 or 25 mg twice daily) in patients with normal renal function serious adverse reactions are very rare. Occasionally patients may develop a skin rash, characteristically morbilliform, and more rarely loss of taste.

Hyperkalaemia Owing to the fall in aldosterone secretion there is a slight rise in plasma potassium with captopril. This is usually of benefit, particularly when captopril is combined with small doses of diuretics. However, in patients with severe renal failure, particularly those being treated with potassium-sparing diuretics such as spironolactone, there may be a marked rise in plasma potassium. Patients with severe renal failure should have plasma potassium monitored carefully during the first few weeks.

Other converting-enzyme inhibitors Some rare but serious side-effects of high dose captopril, proteinuria and agranulocytosis, were thought to be due to one of its constitutents, the sulphydryl group. Several converting-enzyme inhibitors have now been developed without a sulphydryl group.

Enalapril This is a nonsulphydryl ACE inhibitor, which has a similar action to captopril. The other differences are that it is a pro-drug that is converted in the liver to its active form, and it is longer-acting than captopril, so that it can be given once daily. Experience with this drug so far is more limited than with captopril and as it has not been given in high dosage to patients with renal failure or connective tissue disorders it is not possible to say whether it shares the very rare adverse reactions reported with high doses of captopril. Both captopril and enalapril at the low doses now used are remarkably well tolerated by patients.

Lisinopril This non-sulphydryl ACE inhibitor is the lysine analogue of enalaprilat, the active metabolite of enalapril.

	Normal daily dose
Captopril	12.5 – 50 mg twice daily
Enalapril	2.5 – 20 mg once or twice daily
Lisinopril	10–20 mg once daily

Table 11.7 Dosage for angiotensin-converting enzyme inhibitors.

Unlike enalapril, lisinopril is not a prodrug and as such does not require metabolism for its pharmacological activity. It is not metabolized to any detectable extent and is cleared solely by the kidney via glomerular filtration. It is longer acting than captopril and may be used once daily in hypertension.

Although experience is limited, clinical studies indicate that it is an effective antihypertensive agent with a usual maintenance dose of up to 20 mg once daily. Like other ACE inhibitors, it appears to be remarkably well tolerated by patients.

When should ACE inhibitors be used? The major indication for captopril or enalapril is in patients who do not respond to a beta-blocker with a diuretic or in patients in whom beta-blockers are contraindicated, or in those who have developed side-effects. In severe hypertension not controlled by conventional therapy—for example, beta-blocker, diuretic and direct arteriolar vasodilator–converting-enzyme inhibitors may also be very effective combined with either a diuretic or a calcium-entry antagonist. They may also be used in malignant hypertension. As more experience is gained they are now being increasingly used as first-line drugs in mild to moderate hypertension.

Heart failure with high blood pressure Patients with these two conditions may do particularly well with captopril, often showing a remarkable improvement in symptoms. They should be administered cautiously in patients with severe heart failure who are already receiving diuretic therapy, as the initial fall in blood pressure may be rapid.

Scleroderma Patients with scleroderma and malignant hypertension develop rapidly progressive renal failure. Recent reports suggest that captopril may reverse or halt the deterioration in renal function.

Renal artery stenosis The converting-enzyme inhibitors will be effective in lowering blood pressure in renal artery stenosis, but in some patients with bilateral renal artery stenosis or unilateral renal artery stenosis with only one functioning kidney the drugs may cause a deterioration in renal function: indeed, this has been suggested as a diagnostic test. They should be used in this situation with caution, although the deterioration in renal function is usually reversible when the drug is stopped.

1 Skin rash

2 Taste disturbances (very rare with lower doses)

3 Large fall in blood pressure if patient is grossly volume deleted or in some patients with renal artery stenosis

4 Irritating cough

Table 11.8 Side-effects of angiotensin-converting enzyme inhibitors.

	Normal daily dose
Methyldopa	250 – 750 mg twice daily
Clonidine	50 – 500 µg twice daily
Reserpine	100 µg once daily

Table 11.9 Dosage for central acting agents.

Combination therapy

Both captopril and enalapril can be used alone, and if necessary with diuretics. There is some controversy about whether these agents are additive to beta-blockers. Beta-blockers inhibit renin release and ACE inhibitors block the formation of angiotensin II. Beta-blockers may prolong the action of captopril. In patients with angina there is no contraindication to the use of captopril or enalapril.

CENTRAL ALPHA-RECEPTOR STIMULATORS

During the 1960s methyldopa became the most commonly used antihypertensive drug after the diuretics. It was thought that by inhibiting the enzyme that converted dopa to dopamine it would also inhibit the synthesis of noradrenaline, so reducing sympathetic activity and blood pressure. Recent research has shown that both methyldopa and clonidine probably lower blood pressure by central alpha-receptor stimulation. They are effective in lowering blood pressure and are additive to diuretics and arterial vasodilators.

Methyldopa

There are still large numbers of patients who were started on methyldopa in the 1960s and 1970s and have learned to live with the side-effects described below, or may not have even noticed them. Our view is that all patients receiving methyldopa should be offered a trial of alternative therapy. Where beta-blockers or thiazides were contraindicated, for example, for patients with bronchospasm, methyldopa was an alternative drug. If the total daily dose is kept below 1000 mg, side-effects are less common. However, the calcium-entry antagonists and converting-enzyme inhibitors should be used in patients where there are contraindications to beta-blockers and diuretics.

Side-effects Nearly all patients notice that they feel sleepy, particularly during the first few weeks of therapy, and many feel somewhat debilitated. This is likely to become apparent to patients who have been on longterm methyldopa therapy when they stop the drug and suddenly feel much better. The drug may also cause erectile impotence.

There are several serious drug reactions that can occur with methyldopa. These include severe liver dysfunction, a positive direct Coombs' test (although haemolytic anaemia occurs only in fewer than 1 per cent) and drug fever.

Pregnancy Methyldopa is effective in patients with pregnancy-related hypertension and appears to be safe to the fetus. As it is only given for a short time and the side-effects are not severe it remains useful in the treatment of blood pressure associated with pregnancy, although beta-blockers may be preferable (see Chapter 16).

Clonidine

This is very similar to methyldopa. It is an effective drug in lowering blood pressure, but it too causes sedation. Unlike methyldopa it does not cause hepatic and haematological problems. Much more worrying, however, is the rebound hypertension that occurs when clonidine is withdrawn. This is particularly dangerous if patients are also receiving a beta-blocker, when the omission of one dose of clonidine may result in a hypertensive crisis. Because of this and because of the side-effect profile, which is similar to that of methyldopa, clonidine is now hardly used in the UK.

In patients in whom clonidine is being stopped it is important to withdraw the beta-blocker first. It is best to substitute a thiazide diuretic or a vasodilator. Then the dose of clonidine should be reduced

over about seven days before final discontinuation.

ALPHA-RECEPTOR BLOCKERS

Phenoxybenzamine

Phenoxybenzamine is almost exclusively used in patients with phaeochromocytoma, where it can be extremely effective. The usual dose is 10 mg twice daily. In patients with phaeochromocytoma this has to be titrated until control of the blood pressure is obtained, and sometimes larger amounts may be needed; usually a beta-blocker is given concomitantly to control the pulse rate. Phenoxybenzamine has been used as a fourth-line agent in resistant hypertension.

The most prominent side-effects are postural hypotension and problems with ejaculation.

Phentolamine

This is a shorter acting alpha-blocker that is available only by intravenous injection. It is sometimes used to control hypertensive crises in, for example:

- Phaeochromocytoma
- Rebound hypertension following clonidine withdrawal
- Reactions of monoamine-oxidase inhibitors with pressor amines contained in food.

Prazosin

Prazosin was originally thought to be a direct vasodilator but has now been shown to work through its peripheral alpha-adrenergic blocking properties and may be relatively selective for postsynaptic alpha-1 adrenoreceptors. Unfortunately, although it results in peripheral arteriolar vasodilatation there is also some venous dilatation, and postural hypotension may be encountered. This may be responsible for the first-dose hypotension and collapse that is occasionally seen. This can be avoided by giving a low starting dose (0.5 mg) at night. Once the first dose is tolerated, there are few further problems with hypotension. As expected with an alpha-blocker, other side-effects are not uncommon.

Generally prazosin should be reserved as a third- or fourth-line drug for patients not responding to a beta-blocker and/or a diuretic.

Indoramin

This is similar to prazosin but appears to have more side-effects, including a high incidence of failure of ejaculation. Indoramin has no particular advantages over prazosin and should not be used unless there are special indications.

ALPHA- AND BETA-RECEPTOR ANTAGONISTS

Alpha-receptor antagonists and beta-blockers have been used together to treat hypertension. While this combination does lower blood pressure, the side-effects of the alpha-antagonists have often been unacceptable. More recently labetalol, which is both a beta-blocker and a weak alpha-blocker when taken orally, has been introduced. When given intravenously it has greater alpha-blocking properties. Its longterm effect on blood pressure is similar to the beta-blockers although at higher doses the alpha-blocking properties cause postural hypotension. Apart from this, labetalol appears to have no more side-effects than beta-blockers, and is probably no more effective. Some clinicians find it a useful agent, and it has been used to good effect in pregnancy hypertension.

VASODILATORS

The direct arteriolar vasodilators, the first of which was hydralazine, have been used for many years in the treatment of high blood pressure. They all cause a decrease in peripheral vascular tone, with a reflex activation of the sympathetic nervous system leading to an increase in heart rate. They also cause a rise in cardiac output, increased release of renin and higher angiotensin II and aldosterone levels. However, when they are used in combination with a beta-blocker and a diuretic these side-effects are minimized.

Hydralazine

Hydralazine has a direct effect on smooth muscle cells in the peripheral arterioles and only a very small effect on veins. It is largely metabolized in the liver. On its own, it was found not to be very effective in lowering blood pressure because of the reflex sympathetic stimulation and the high doses needed.

Hydralazine has been extensively used as a third-line drug in patients with more severe hypertension who do not respond to a beta-blocker in combination with a diuretic. It is also used in patients with renal failure. While hydralazine has, until recently, been the most commonly used third-line drug, nifedipine and captopril are now becoming more popular. It is likely that the use of hydralazine will decline now that nifedipine, enalapril and captopril are being more widely used.

Dosage As with many other older blood pressure drugs, hydralazine was initially given in excessively high doses. It is best to start with 25 mg twice daily, increased to 50 mg twice daily. Above this level there is a greater risk of side-effects. Patients who do not respond or who require higher doses of hydralazine may be fast hepatic acetylators who metabolize the hydralazine more quickly. Slow acetylators develop a greater antihypertensive response, but suffer more side-effects.

Alpha-adrenoceptor blockers	Normal daily dose
Phenoxybenzamine	10 – 50 mg once or twice daily
Prazosin	0.5 – 5 mg three times daily
Indoramine	25 – 100 mg twice daily
Alpha and beta-receptor antagonists	
Labetalol	200 – 2000 mg twice daily

Table 11.10 Dosage for alpha-adrenoceptor blockers and alpha and beta-receptor antagonists.

	Normal daily dose
Hydralazine	25 – 100 mg twice daily
Minoxidil	2.5 – 20 mg twice daily
Diazoxide	injection only 100–300 mg

Table 11.11 Dosage for peripheral vasodilators.

Side-effects Many patients, particularly the younger ones, develop symptoms of peripheral vasodilatation including headaches, flushing and palpitations. These may be overcome by combining hydralazine with a beta-blocker. Some patients develop a lupus-like syndrome with arthritis, pyrexia and general malaise. This usually occurs at higher doses or in patients who are slow acetylators. It is usually fully reversible by withdrawal of the drug. If the dose of hydralazine is kept below 100 mg daily, the lupus syndrome is rare. It may also be under-recognized if the arthritic symptoms are mild.

Minoxidil

This is one of the most potent vasodilators known. Its mode of action is similar to that of hydralazine, and it similarly causes tachycardia owing to reflex sympathetic stimulation. It also always causes sodium and water retention, leading to oedema. In view of the side-effects it has largely been reserved for men with uncontrolled hypertension. With the increasing use of captopril and the calcium-entry antagonists the use of minoxidil has diminished.

Sodium and water retention can be prevented by the use of diuretics. Frusemide is almost always needed, often in large doses. The tachycardia means that beta-blockers are also always needed. The other serious side-effect is a generalized increase in hair growth, particularly on the forehead and temples. This hirsutism virtually precludes its use in women (see Chapter 12).

Dosage The usual starting dose is 2.5 mg twice daily. It may be necessary to increase the dose to 15 mg twice daily. There is some doubt as to whether it is possible to give minoxidil in a single dose once daily, but in combination it may be long-acting.

Diazoxide

Oral diazoxide is now hardly used, although it is still available in Britain. It is a potent vasodilator that has similar side-effects to minoxidil. It may also induce acute diabetes mellitus and a Parkinsonian syndrome. This drug is no longer needed, since the introduction of minoxidil, nifedipine and captopril.

OTHER HYPERTENSIVE DRUGS

Rauwolfia alkaloids

These drugs have both central and peripheral effects on noradrenaline release. They are not much used now in Britain because of their side-effects.

Reserpine

Reserpine was once widely prescribed and found to be effective both when used alone and when combined with a diuretic. When given in a low dose (0.1 to 0.2 mg) at night, side-effects are not serious. However, at higher doses it causes sedation and depression, even leading to suicide. Consequently it has been largely abandoned in Western countries, particularly since the introduction of methyldopa. Nevertheless, worldwide, it is still commonly used in combination with a diuretic and hydralazine. It remains the treatment of choice in many Third World countries, because of its low cost.

Postadrenergic blockers (guanethidine, bethanidine and debrisoquine)

These drugs can be considered together as they have similar effects. Although they are effective in lowering blood pressure, they have serious side-effects:

- Severe exercise-induced and postural hypotension
- Failure of ejaculation, sometimes impotence and rarely severe diarrhoea.

These drugs should therefore no longer be used and patients already on them should be changed to more modern treatment.

PRACTICAL POINT

- Thiazides, beta-blockers, calcium blockers and ACE blockers are all acceptable first-line antihypertensive therapy.

12
Schemes for reducing blood pressure

BACKGROUND

There are well over one hundred different drugs that lower blood pressure with approximately twenty different mechanisms of action. New types of drugs and new formulations or combinations of existing agents are continually being developed.[1] It is not surprising, therefore, that there is some disagreement even between experts about which drugs or combinations of drugs are best for individual patients. Often, by the time definitive evidence of the usefulness of one particular group of drugs has become available, new products have been developed that may have advantages or fewer side-effects.

Some drugs may have added beneficial effects or fewer harmful effects which are independent of their blood pressure lowering action. For example, whilst the thiazide diuretics have few clinical side-effects, their metabolic effects on potassium, glucose and lipids continue to cause concern. Conversely, the beta-receptor blockers despite their side-effects may have some protective effect against cardiac disease in selected cases. However, despite the many important differences between the various types of antihypertensive agents it is probably true that it does not really matter how blood pressure is reduced, but it must be reduced, and with the minimum of side-effects. Unfortunately about one half of all patients receiving antihypertensive drugs have inadequate control of their blood pressure.

During the last decade the treatment of most forms of hypertension was relatively simple; patients were started on either a beta-blocker or a thiazide diuretic, and if one drug was insufficient the two were used in combination, and further drugs were then added in sequentially. This so-called 'step-care' approach has recently been overtaken by the advent of the angiotensin-converting (ACE) inhibitors and the calcium-entry antagonists, which are now being used as second or first-line drugs. As further experience is gained it is becoming clear that individual patients respond to different drugs in different ways so that rigid schemes for blood pressure reduction are not appropriate. In this chapter we outline our current practice in treating hypertensive patients.

The goal of antihypertensive therapy

The clinician's objective in drug therapy should be to reduce the blood pressure to the normal range (below 90 mmHg diastolic pressure), at the same time leaving the patient feeling completely well. The better the control of the pressure the lower is the risk of premature death or illness from cardiovascular, cerebrovascular and renal disease. The more severe the hypertension the greater is the risk of death, but greater too are the benefits of treatment.

In general the same drugs are used whatever the level of blood pressure, but in more severe cases there is a greater urgency for reduction of the pressure so there may be little time initially to estab-

lish the best approach for the individual patient. However, the urgency of treatment is commonly over-stressed and, apart from cases with encephalopathy, gross left ventricular failure or aortic dissection, there is no need to reduce blood pressure over minutes or hours. Even in malignant hypertensives, blood pressure should be lowered only over twenty-four to forty-eight hours, and in that period it should not be reduced to normal. In such cases pressure should be normalized over a few days. Over-rapid blood pressure reduction can be as dangerous as a very high blood pressure left untreated.

BLOOD PRESSURE LOWERING REGIMES

Non-pharmacological blood pressure reduction All patients should be instructed on non-pharmacological ways in which blood pressure may be lowered (see Chapter 10). Paradoxically, non-pharmacological treatment is most often stressed to patients with only mild hypertension where these measures are less effective. Patients with more severe hypertension should also be instructed on how they can help to lower their blood pressure by salt restriction, and where relevant by weight loss and moderation of alcohol intake. Salt restriction is known to have a useful additive effect to many antihypertensive drugs.

First-line antihypertensive drug therapy There are now at least four possible first-line antihypertensive drug groups. These are the thiazide diuretics, the beta-blockers, the calcium-entry antagonists and the ACE inhibitors. If any one of these causes side-effects or is ineffective another type should be substituted or added. If the blood pressure is still not satisfactorily controlled, different combinations of antihypertensive agents are added in until the optimum blood pressure is achieved.

THE FIRST STEP

Diuretics

There are no basic differences between the many thiazide diuretics. If this group of drugs is to be used then the best option is to prescribe the cheapest, and at the lowest possible dose. It is our practice to use either bendrofluazide in a single daily dose of 2.5 mg or hydrochlorothiazide (12.5 mg–25 mg daily) as this minimizes the clinical and metabolic side-effects.[2]

Thiazide diuretics are most useful in:

- Older patients
- Black patients
- Patients with mild or incipient heart failure

They are best avoided in:

- Maturity onset diabetics
- Patients with hyperlipidaemia
- Pregnancy
- Patients with gout

They should be discontinued in:

- Men complaining of impotence
- Patients developing hyperglycaemia or hyperlipidaemia.

Patients receiving diuretics of any type should have their serum electrolytes checked after about two months and thereafter at least annually. It is not our practice to prescribe potassium supplements. Combined diuretic and potassium chloride tablets should not be used as they contain small amounts of potassium. If the serum potassium falls then the potassium sparing diuretics (amiloride, triamterene or spironolactone)

may be added. The addition of a beta-blocker or an ACE inhibitor to a low dose of a thiazide diuretic also blunts the fall in serum potassium. Patients on longterm thiazide therapy should have occasional checks of their urine or blood for glucose and their serum lipid levels should be checked. If marked hypokalaemia develops with the use of thiazide diuretics, a diagnosis of primary hyperaldosteronism should be considered.

Beta-blockers

The differences between many beta-blockers are not great.[3] The main advantages of this group of drugs are that they can usually be given in a single once-daily dose, there are no major problems with toxicity and most of the contraindications are well recognized. As with the thiazide diuretics it is generally advisable to use the lowest dose. Only rarely does increasing the dose lead to improved blood pressure control.

Beta-blockers are most useful in:

- Younger patients
- Anxious patients
- Non-smokers
- Patients with renal insufficiency
- Pregnancy
- Angina pectoris
- Patients who have had a myocardial infarction

Beta-blockers should be avoided in:

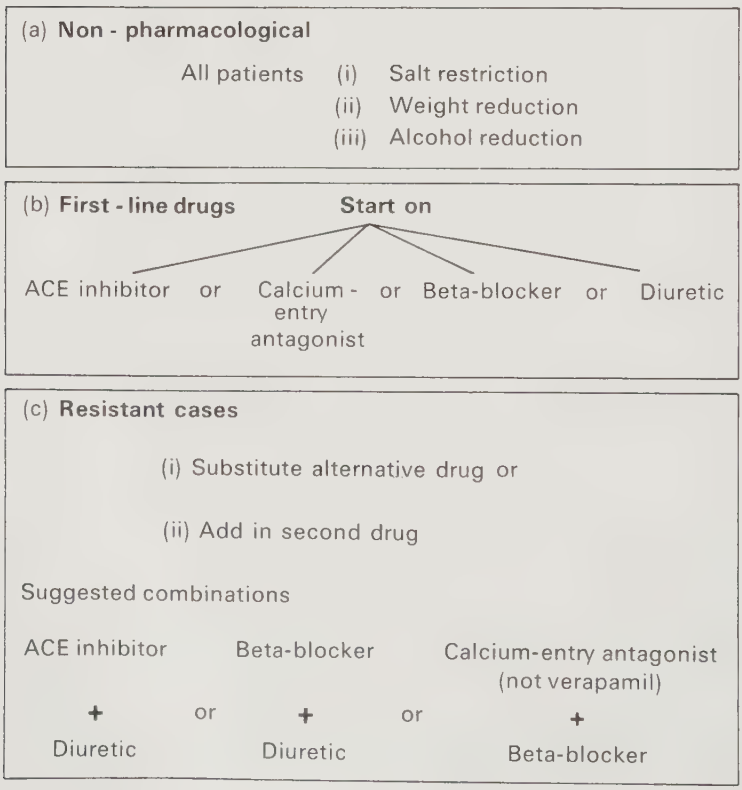

Figure 12.1 A guide to blood pressure treatment.

- Asthmatics
- 'Brittle' insulin-requiring diabetic patients
- Intermittent claudication
- Raynaud's syndrome
- Second and third degree heart block
- Patients with heart failure

Beta-blockers should be discontinued in:

- Patients developing heart failure
- Patients developing asthma
- If the pulse rate falls to below 48 beats per minute.

The minor differences between the beta-blockers mean that the clinician may favour one particular drug in an individual case. However, if major problems develop with one beta-blocker, it is likely that they will also be encountered with other members of the group.

Hydrophilic beta-blockers (atenolol, nadolol and sotalol)
- May cause less tiredness and loss of exercise tolerance
- Should be given in lower dose in patients with renal failure

Cardioselective beta-blockers (atenolol, acebutolol, metoprolol)
- May have fewer effects on airways resistance
- May cause less interference with the autonomic and metabolic responses to hypoglycaemia in insulin-dependent diabetic patients

Intrinsic sympathomimetric activity beta-blockers (oxprenolol, pindolol, acebutolol)
- May cause less reduction of peripheral bloodflow.

As discussed elsewhere (see Chapter 11), there was at one stage considerable optimism that the beta-blockers would have special advantages over other agents by having a 'cardioprotective' effect. Recent evidence has proved disappointing except in non-smokers, where a beneficial effect has been found. This advantage is still, therefore, to be gained by hypertensive patients who do not smoke and this evidence further emphasizes the importance of persuading patients to stop smoking.

Calcium-entry antagonists

There are two distinct types of calcium-entry antagonists: those that are principally arterial vasodilators (such as nifedipine and diltiazem) with little effect on the heart and those (such as verapamil) that also slow the heart rate.[4] While these are not new drugs their use as first-line therapy in hypertension is a relatively novel approach. Nifedipine should be used in the 20 mg tablet 'retard' formulation, given twice daily.

Nifedipine is most useful in:

- Older patients
- Black patients
- Patients with peripheral vascular disease
- Patients with cerebrovascular disease
- Patients with angina pectoris

Verapamil is most useful in:

- Patients with concurrent tachyarrhythmias
- Angina pectoris

Verapamil should be avoided in:

- Patients with cardiac failure
- Any degree of heart block.

A disadvantage of nifedipine and nicardipine is that they cannot, at least in the present formulations, be used in a once daily dosage. While nifedipine is a very effective drug, approximately 10 to 15 per cent of patients prescribed it are unable to tolerate it owing to the side-effects of flushing, headache and occasionally diuretic-resistant ankle oedema. Several new calcium-entry antagonists will soon become available. It is not yet clear whether they will have any special advantages.

Angiotensin-converting enzyme (ACE) inhibitors

This group has the fewest side-effects of all the blood pressure lowering drugs.[5] Apart from the once daily prescription of enalapril it is doubtful whether there are any major differences between the ACE inhibitors when used in the correct dosage.[6,7]

ACE inhibitors are particularly useful in:

- Younger patients
- Patients with incipient or mild heart failure
- Patients who develop side-effects from other drugs

ACE inhibitors should be used with care in:

- Renal artery stenosis
- Severely fluid-depleted patients, especially those already receiving a loop diuretic such as frusemide, unless the diuretic is stopped.
- Avoid in pregnancy.

The lowest possible dose should be used to initiate therapy, e.g., 12.5 or 25 mg captopril, 2.5 or 5 mg enalapril or lisinopril. The maximum with captopril should not exceed 100 mg and enalapril and lisinopril 40 mg daily.

Centrally acting antihypertensive drugs

This group is at present out of favour. While clonidine certainly should never be used, both methyldopa and reserpine do have a role in selected cases. The major side-effects of sedation and depression can be minimized if these drugs are used in low doses. However, both should be used as last-resort first-line drugs.

Other antihypertensive agents

It is not our practice to use alpha-blocking drugs (indoramin, phenoxybenzamine and prazosin), adrenergic blockers (guanethidine, bethanidine and debrisoquine), direct vasodilators (hydralazine, minoxidil and diazoxide) or non-thiazide diuretics (loop diuretics or potassium retaining agents) as first-line therapy. Occasionally patients are encountered taking drugs such as reserpine, methyldopa or prazosin who are entirely well, with good blood pressure control. It is then justifiable to continue these drugs' use.

THE SECOND STEP

If optimum control of blood pressure is not achieved with the first-line drugs used appropriately and in the correct dose, then it is usual to add in another type of antihypertensive agent. Most can be used together but there are some combinations which are not particularly effective or are potentially harmful.

Commonly used drug combinations

1. Thiazide diuretic with added:
   beta-blocker
2. Beta-blocker with added:
   thiazide diuretic
   nifedipine or diltiazem
3. Nifedipine or diltiazem with added:

beta-blocker
ACE inhibitor

4. ACE inhibitor with added:
   thiazide diuretic
   calcium-entry blocker
   beta-blocker

Drug combinations which may be hazardous or pointless

1. Beta-blocker with verapamil
2. Two drugs of the same class used together.

THE THIRD STEP

Patients whose blood pressure is resistant to double therapy in the combinations suggested above have a high risk of the cardiovascular complications of hypertension. It is advisable for such cases to be referred to specialist blood pressure clinics, particularly as it is important to exclude an underlying cause for the hypertension. The policy in resistant hypertensive patients is to:

Check compliance
Enquire whether the patient is taking the prescribed drugs and whether he finds the tablet regime difficult to remember. Lack of compliance is suggested where there is no fall in pulse rate in patients taking beta-blockers, or no fall in serum potassium in those receiving thiazides alone.

Simplify the antihypertensive regime
Complex regimes can lead to poor compliance. It is reasonable to convert patients to once daily regimes and single tablet diuretic/beta-blocker combinations are justified. No regime for any patient need be more frequent than twice daily.

Give advice on salt restriction
A rough guide to a patient's usual sodium intake can be obtained from a twenty-four hour urine collection for electrolytes. Specific advice from a dietitian may be helpful.

Weight reduction Where relevant give advice on weight reduction and moderation in alcohol intake.

Check for underlying remediable causes of hypertension (see Chapter 8).

Triple-therapy drug regimes
The therapeutic principles of managing resistant hypertension are the same as for milder grades; it is usual to add in a third drug of a different class.

Regimes used in resistant hypertension

1. ACE inhibitor plus nifedipine, diltiazem or verapamil, plus frusemide
2. Beta-blocker plus nifedipine or diltiazem plus a thiazide diuretic
3. ACE inhibitor plus frusemide plus beta-blocker
4. Beta-blocker, diuretic, nifedipine or diltiazem and ACE inhibitor
5. Beta-blocker plus frusemide plus minoxidil
6. Beta-blocker plus diuretic plus alpha-blocker (e.g., prazosin).

Minoxidil is a very powerful vasodilator but its side-effects necessitate the concurrent use of both a beta-blocker and a loop diuretic. Increased facial hair growth precludes this drug in women.

Hydralazine is a less powerful vasodilator, and if the total daily dose is kept below 100 mg there are fewer side-effects. It may be usefully added to a beta-blocker/thiazide combination.

In patients receiving a beta-blocker with a vasodilator, the substitution of frusemide for a thiazide diuretic may be helpful, especially if there is evidence of undue weight gain after treatment has been started.

Patients receiving an ACE *inhibitor* can, with care, be given increasing doses of frusemide. At very high doses of frusemide, postural hypotension may be a problem. The combination of an ACE inhibitor with a calcium-entry antagonist may be as effective.

It is sometimes helpful to add in the aldosterone antagonist spironolactone to triple-therapy regimes that include a thiazide or loop diuretic.

Most of the regimes described above are complex and it is important that they are built up gradually.[8] In some cases it is helpful for the patient to be admitted to the hospital so that changes can be made every few days, but it should be remembered that in-patient blood pressure readings obtained with the patient resting may be very misleading, and out-patient blood pressure readings may still be uncontrolled.

Occasionally a patient is encountered whose blood pressure, while never dangerously high, appears to be resistant to all treatment. It is worth checking whether the patient has only transient elevations of pressure in response to attending the clinic. If he or she is rested in a quiet room for half an hour and the blood pressure is checked by a reliably trained nurse, lower readings may be obtained. If such patients have absolutely no evidence of cardiac, renal or cerebral damage, and particularly if the ECG shows no evidence of left ventricular hypertrophy (RV5 + SV1 less than 35 mm) or left atrial dilatation (biphasic P wave in lead V1), then it may be reasonable to accept less-than-optimal control of blood pressure in the clinic. In such cases, home blood pressure monitoring, possibly with an automatic sphygmomanometer, may confirm that pressures are low when the patient is away from the potentially threatening clinical environment.

(a) **Check compliance with lifestyle changes**
  (i) salt restriction
  (ii) weight reduction
  (iii) alcohol restraint

(b) **Check therapeutic compliance**
  (i) tablet counts
  (ii) monitor drug levels in blood if possible
  (iii) simplify therapeutic regime

(c) **Investigate further for underlying cause of hypertension**
  (i) Renal arteriogram (even if IVP is normal)
  (ii) Urinary catecholamines

Figure 12.2 A guide to resistant blood pressure control (i.e., not controlled by two drugs).

MALIGNANT HYPERTENSION

All patients with the malignant phase of hypertension (i.e., those with retinal haemorrhages or exudates, with or without papilloedema) should be admitted to the hospital as soon as possible for controlled blood pressure reduction as well as detailed investigation of their hypertension. If blood pressure is not adequately reduced, the disease progresses rapidly to end-stage chronic renal failure requiring dialysis or to death from cardiac failure or stroke. As with other grades of

hypertension, the outlook is closely related to the quality of care during the weeks and months following diagnosis. The five-year survival rate for malignant hypertension should now be around 80 per cent.

Perfect control of blood pressure should be achieved over a period of a few weeks as more rapid treatment can lead to acute reductions of bloodflow to the brain and kidneys, causing cerebral infarction or deterioration of renal function. The aim should be to lower the diastolic pressure with the use of oral therapy only[9] to around 110 mmHg over a period of twenty-four to forty-eight hours, and to lower it to below 90 mmHg only after a week or two, often after the patient has been discharged from hospital.

Regimes for malignant hypertension

1. Atenolol 50 or 100 mg in a single oral dose, and thereafter 100 mg daily (see Figure 12.3)
2. Captopril—initially 6.25 mg followed by 25 mg twice daily
3. Nifedipine 10 or 20 mg in a single oral dose and thereafter 20 mg twice daily.

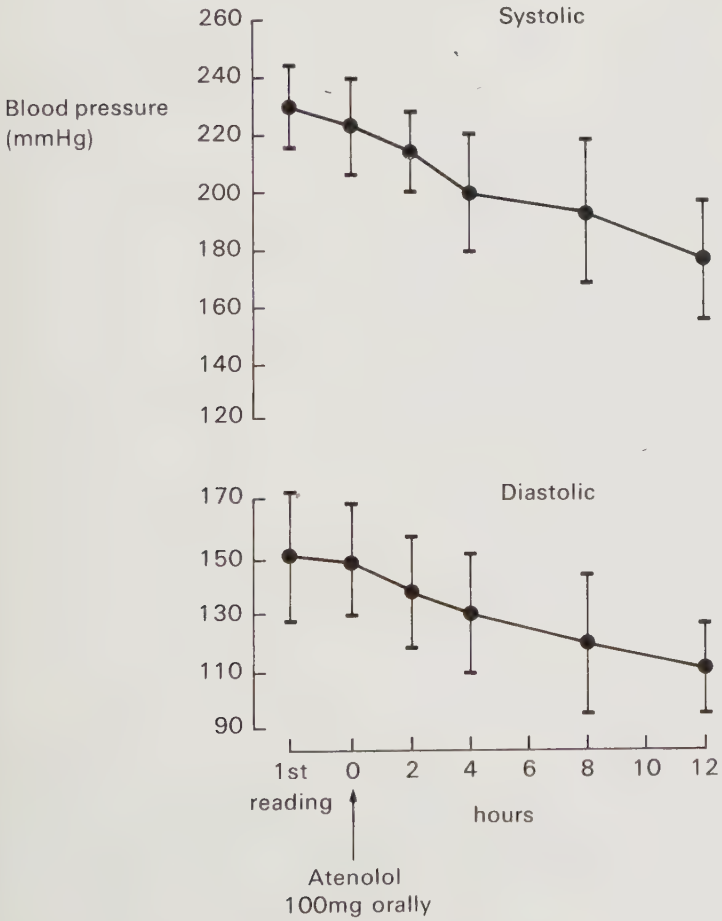

Figure 12.3 The effect of a single dose of oral atenolol (100 mg) on systolic and diastolic pressure in ten patients (from *Brit. Med. J. 282*, 1981, 1757–8).

These are suitable for most cases of malignant hypertension. Parenteral antihypertensive drugs are never justified unless the patient has severe heart failure or hypertensive encephalopathy.

After the first few days the principles of managing malignant hypertension are the same as for more routine cases, although triple therapy is almost always necessary. These patients are best supervised on a

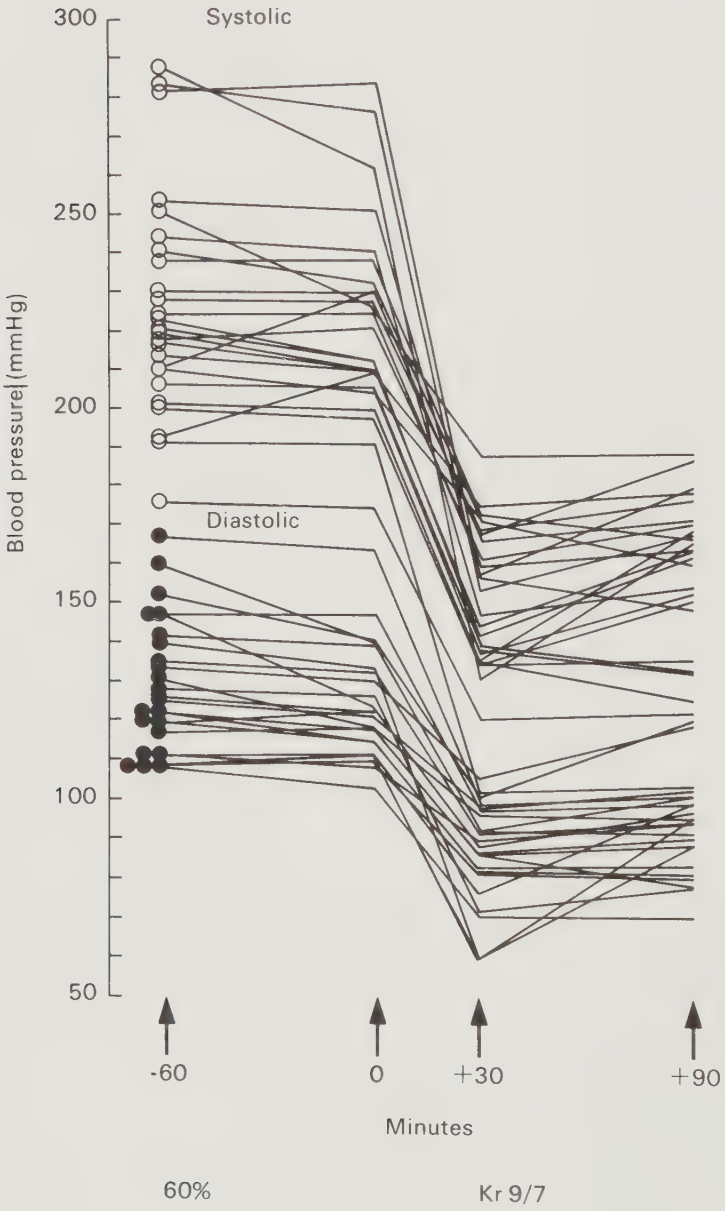

Figure 12.4 The effect of a single 10 or 20 mg capsule of nifedipine on systolic and diastolic blood pressure (from *Brit. Med. J. 286*, 1981, 19–21).

longterm basis by physicians with a special interest in hypertension.

HYPERTENSIVE EMERGENCIES

Many blood pressure lowering drugs can be given intravenously or intramuscularly and they lower blood pressure very rapidly. Their only indication is in the treatment of hypertensive encephalopathy or gross ventricular failure directly due to raised blood pressure or dissecting aortic aneurysm.[10]

Diazoxide

This drug has been widely used as a parenteral agent. Some years ago it was recommended to be given rapidly as an intravenous bolus of 300 mg. This produces an immediate fall in blood pressure of 30 to 40 per cent within two or three minutes and serious complications have been described. A much better way of giving diazoxide is either by infusion or in 50 mg intravenous boluses every ten minutes, the dose being increased as necessary until adequate blood pressure control is reached. Using this method the blood pressure may be reduced over thirty minutes to two hours to the desired level avoiding precipitous falls.

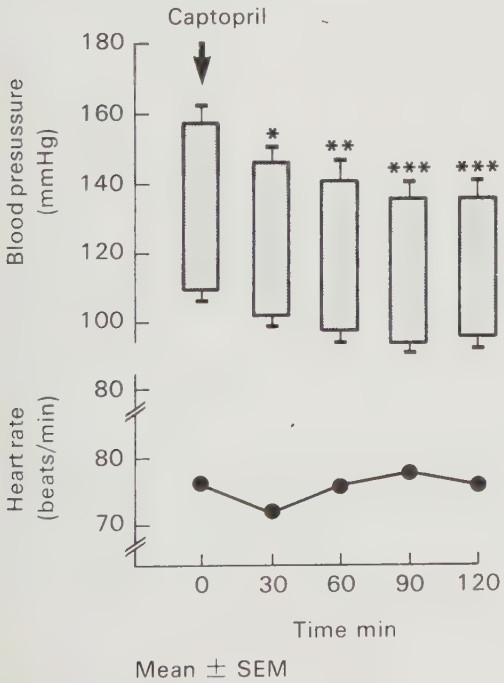

Figure 12.5 The effect of a single dose of captopril (25 mg) on systolic and diastolic blood pressure in twenty-two patients (from *Brit. J. Clin. Pharm. 14*, 1982, 1215–65).

Labetalol

When given by intravenous infusion, labetalol has a predominant alpha-blocking effect and lowers blood pressure rapidly but can cause severe postural hypotension. It is not therefore to be recommended for parenteral therapy. Intravenous boluses of labetalol have an even more unpredictable effect.

Nitroprusside

This is a potent vasodilator that invariably lowers blood pressure when given by intravenous infusion. The fall in blood pressure is controlled by the rate of infusion. It must be given under very close supervision as severe hypotension can occur. As well as causing the expected side-effects of any arteriolar vasodilator, including flushing and postural hypotension, nitroprusside is metabolized to cyanide and thiacyanate. This is not important during short-term infusion but toxicity can develop if the drug is given over several days, particularly if there is renal failure.

New solutions need to be made up to every four hours and must be covered by light-proof paper to prevent photo-deactivation. The starting dose is 0.5 μg/kilogram/minute. For a 70 kg (150 pound) patient this means starting at 3.5 μg/minute but the dose can gradually be increased to 200 μg/minute. Blood

pressure should be measured frequently, preferably using an automatic manometer, and great care must be taken to avoid precipitous falls in pressure.

Hydralazine

Hydralazine can be given either intravenously or intramuscularly and is widely used, particularly in obstetrics. The normal dose is 10 to 40 mg injected slowly. In most situations where it is used, oral hydralazine would be just as effective.

Oral therapy

For patients able to take drugs by mouth, most blood pressure lowering drugs given orally act rapidly. For instance, nifedipine given in a 10 mg capsule, either bitten and held under the tongue or even swallowed, will cause blood pressure to fall within ten to fifteen minutes (see Figure 12.4). The ACE inhibitor captopril when taken orally lowers blood pressure within thirty minutes (see Figure 12.5), although enalapril has a slower effect on blood pressure since it must be converted by the liver to an active metabolite. Oral beta-blockers with or without hydralazine reduce blood pressure over a period of two to three hours.

PRACTICAL POINTS

- Antihypertensive regimes are now more complex than they used to be, mainly because of the wide choice of agents. It is, however, now usually possible to control blood pressure with relatively few side-effects and regimes can be tailored for patients with specific problems. (The problem of blood pressure reduction in patients who have concomitant diseases is discussed in Chapter 14.)
- The goal of therapy in all patients up to the age of about seventy-five years is to reduce the diastolic blood pressure to below 90 mmHg.
- The outlook depends on the quality of patients' blood pressure control rather than on the initial severity of their hypertension.
- If optimum control of pressure is not obtained, patients should be referred for further treatment to physicians who have a special interest in hypertension.

13
Hypertension in primary medical care

BACKGROUND

Other chapters in this book have dealt with the value of the investigation and reduction of high blood pressure. The next question is, who should actually deliver this potentially life-saving treatment? There is evidence that the quality and efficiency of blood pressure reduction is a more potent predictor of a patient's life expectancy than the severity of the hypertension in the first place. Regrettably, practically every population survey in the UK, the USA and elsewhere has reported a depressing and woeful state of underdiagnosis, undertreatment and inadequate follow-up of hypertensive patients. The 'rule of halves' described in Chapter 1 means that less than 15 per cent of all hypertensives are receiving adequate clinical care. The need for improvement in detection and management of hypertension ranks with the abolition of cigarette smoking as a major public health concern in developed countries. In developing countries this new epidemic is just around the corner.

The responsibility for the organization of case detection, treatment and follow-up of hypertensive patients must rest with the primary health care team, in the context of good general or family practice. This chapter contains the justification for this view and suggestions for its organization.[1]

SCREENING FOR HYPERTENSION

As outlined in Chapter 1, hypertension is an eminently suitable disease for some form of screening programme. The exact method employed depends on the health care facilities available in individual countries.

Selective screening

A very strong case has been made for selective screening of people who are at particular risk.

Family history It should be the responsibility of patients and doctors alike to seek out symptomless relatives of patients with hypertension or its complications, particularly heart attack and stroke, who may benefit from antihypertensive treatment.

Pregnancy Another high-risk group are pregnant women; here the efficient detection and management of high blood pressure is already an integral part of good obstetric care (see Chapter 16). The rest of the medical profession have a lot to learn from this.

Previous complications Patients who have already suffered a vascular complication of hypertension have a very high risk of recurrence. Second strokes can be prevented if blood pressure is controlled on a longterm basis.

The routine selective screening of survivors of heart attacks or strokes once they have gone home must be regarded as an integral part of good clinical care.

Mass screening

The so-called 'well population screening' of fit populations is an emotive issue. Screening alone is not enough; there must also be efficient follow-up of abnormalities detected. This means that the establishment of screening programmes is expensive. Mass screening using mobile screening buses is an efficient means of recruiting patients for clinical trials, but obviously this one-off exercise cannot solve a longterm problem.

Occupational screening

Screening of employees clearly has its place but this is available only to a minority of the population, mainly men who are employed in large firms or industries. There are also problems of confidentiality of clinical information, and usually industrial medical officers do not organize follow-up or drug treatment.

Casual screening

The provision of blood pressure measurement equipment and staff in supermarkets, department stores and public places can make only a small impact without follow-up and treatment. There is evidence that casual screening programmes such as these tend to attract hypertensive patients who are already diagnosed; people whose pressures have never been measured tend to ignore them. Increased public health education may alter this tendency, but the system is certainly not ideal at present.

Screening by the primary health care team

In an ideal world every person from childhood upwards would have his or her blood pressure measured. Screening people below the age of about thirty would, however, yield relatively few hypertensive cases. Furthermore, the benefits of intervention in very mild hypertension in childhood and adolescence are unknown. People examined over the age of seventy-five would produce a very large number of abnormalities, but this would be in a group of patients in whom the benefits of therapy of mild hypertension are less certain.

A reasonable compromise is for case detection programmes to be instituted for everyone between the ages of thirty-five and seventy. This represents about 980 examinees in an average general practice in Britain, which has about 2300 people on each practitioner's list. Of those examinees about 20 to 25 per cent (190 to 240 people) will have diastolic pressures at first screening of 90 mmHg or more. As many blood pressures settle on rechecking, after three visits between 100 and 120 patients are likely to have blood pressures within the range requiring antihypertensive treatment.

In developed countries, more than 75 per cent of the adult population see a doctor for some reason over a period of three years and initial screening can be carried out at these visits.[2] The organization of family medicine varies from place to place and from country to country, but there are several ways in which individual doctors or groups of family doctors may organize their case detection programmes.

Case detection of patients as they present

All this requires is for the doctor, or the practice nurse or receptionist, to check that there is a recent blood pressure reading in the records of all attenders. The system is simple and continuous and,

most important, feasible for every family doctor's practice.

Appointments for eligible examinees

A faster way is to arrange appointments for all patients considered at risk to have a routine blood pressure check. This will require extra paperwork and time spent on screening clinics. However, it can achieve a complete screen over a period of a few months. The primary care team should therefore consider sending appointments to all men and women for blood pressure checks. At the same time, 'well woman' and 'well man' health checks can be made including examination for breast lumps, cervical cytology, urine testing and possibly screening for hypercholesterolaemia.

Screening of newly eligible patients

Once the backlog of previously unscreened patients has been examined it is important to continue the programme to include individuals who become eligible for screening over the ensuing years. For this purpose, the doctor should ideally have an age/sex register of the patients on the practice list. Patients reaching the age of thirty-five can thus be summoned for screening. One general practitioner in England sends his patients a birthday card together with an appointment for a blood pressure and health check.

In addition, when a new patient joins the list an appointment should be arranged for a medical check.

Medical records

Any attempt to establish a systematic case detection programme requires good medical records. In the UK the general practitioner medical records system is adequate, but certain additions are recommended.[3]

Flags Any type of sticker, or protruding section of an inserted card, renders individual patients' records readily identifiable. These can be used to draw attention to important diagnoses, not only of hypertension, and to identify patients due for blood pressure checking.

The system has been used in many practices and it is simple, cheap and effective. With a few hours' work per week a doctor or his secretary or receptionist can in about six weeks go through the medical records and insert flags as needed.

Screening record cards Inside the record folder a separate screening card is useful. Information on smoking habits, weight and other relevant diseases should be included. The card can also be designed to act as a follow-up record sheet, with spaces for subsequent appointments, names of drugs and dosages, general comments and possibly a graphical blood pressure chart. Many such screening and follow-up record cards have been devised by individual doctors and by pharmaceutical companies, and their use is strongly recommended (see Figures 13.1 and 13.2).

Age/sex register A register of patients by age and sex is invaluable as an aid in all preventive medicine. Many groups of family doctors have created their own, to good effect. In the UK, where well over 90 per cent of the population are registered with a National Health Service practitioner, perhaps the most useful assistance given by community health doctors would be to provide general practitioners with an up-to-date computer printout of all patients registered with them. A list of known hypertensives and of patients due for screening would also be useful.

Diagnostic lists Some doctors have found it convenient to keep an updated

card-index of patients diagnosed as hypertensive so that they can easily check, for example, who has been seen, who is receiving drug therapy or how many patients still have inadequate blood pressure control.

Computerization Computerized records are time and space-saving. Microcomputers are now relatively cheap and they can be programmed to store information such as patient lists, appointments, follow-up records, repeat prescriptions and blood pressures. There is an increasing need for manageable commercially produced software for the detection and follow-up of hypertensive patients.

Patient-held records Pilot surveys have demonstrated that patients can be relied upon to carry their own medical records in a single wallet-sized folder. Alternatively, a blood pressure personal record card may be used. These are particularly useful as shared-care record cards for patients who are attending a hospital clinic as well as seeing their family doctor. They aid communication and obviate the need for a great many letters. These cards can display blood pressure readings in tables or graph form together with a list of drugs and dosages. Other relevant information including investigation results and weight can also be included. An additional advantage is their educational role; the patient

HYPERTENSION

SURNAME	FORENAMES	DATE OF BIRTH
ADDRESS		
SUMMARY OF HISTORY		
FAMILY HISTORY		OBSTETRIC HISTORY .....
SMOKING		AVERAGE WEEKLY ALCOHOL INTAKE .....
ANTIDEPRESSIVES	STEROIDS	CONTRACEPTIVE

Figure 13.1 A blood pressure screening card suitable for use in primary medical care. This can also be used as a patient-held record system.

knows his or her blood pressure and the names of the drugs being used, and can see the effect of the treatment.[4]

Who measures blood pressure?

The techniques for blood pressure measurement are covered in Chapter 6. An ordinary well-maintained mercury manometer is all that is needed, and there should be two cuffs: one of normal size and a larger one for obese patients.

In group practices, nurses or receptionists can be trained to measure pressures and to maintain good medical records. This is probably the ideal; paramedical staff, suitably briefed, seem to be more reliable than doctors.[5]

Within a group practice it is best for a single doctor to undertake responsibility for the detection and management of hypertension. He or she should be able to collaborate with local hospital-based specialists in cardiovascular and renal diseases.

LEVELS OF BLOOD PRESSURE REQUIRING ACTION

The present state of knowledge is that antihypertensive drug therapy is justified if a patient's diastolic blood pressure persistently exceeds 95 to 100 mmHg. There is now evidence that therapy is justified in patients up to the age of about eighty (see Chapter 15). However, pati-

DATE	4/6/84	18/6/84	20/7/84	22/8/84	7/9/84	2/10/84	7/12/84
B.P. Sitting/Lying	174/102	172/104	160/92	158/84	162/92	150/86	148/84
PULSE	96	92	68	64	76	72	76
WEIGHT kg st lbs	84·0	83·5	83·0	83·5	84·0	84·5	82·5
DRUG (Dose/Day) 1 PROPRANOLOL		START 40 mg x 2	40 mg x 2	STOP			
DRUG (Dose/Day) 2 ENALAPRIL				START 5 mg daily	10 mg/day	10mg	10mg
DRUG (Dose/Day) 3							
DRUG (Dose/Day) 4							
SERUM UREA	3·6			4·1			
SERUM POTASSIUM	4·1			4·8			
OTHER INVESTIGATION	LIPIDS NORMAL				IVP NORMAL		
TIME TO NEXT VISIT	2/52	4/52	4/52	2/52	5/52	2/12	3/12
COMMENTS	Advice only	must lose weight	tired	very tired	better	must lose wt!	
DOCTOR's SIGNATURE	DW	DW	DW	DW	DW	DW	DW

Figure 13.2 A blood pressure follow-up card suitable for use in hospital and general practice.

ents whose pressures are only just below this dividing line, or whose pressures, having been raised, have settled, also require general advice and, of course, regular rechecking.

Figure 13.3 provides recommendations on procedures at the time of screening. These take into account the increasing prevalence of hypertension with age and the current data on the benefits of treatment. The recommendations in patients below the age of thirty-five and above the age of eighty are included for completeness, although at the moment screening programmes are not recommended.

The recommendations are related to an otherwise symptomless patient attending a screening programme. Clearly they cannot cover every eventuality. It could be argued that all patients should be given good general health advice on weight control, salt reduction, alcohol moderation and, of course, cigarette smoking. If patients' blood pressures are raised, it is only rarely necessary to institute drug therapy on the basis of a single reading, and patients with such very high blood pressures should probably be admitted to hospital anyway.

In most cases blood pressures should be rechecked at a second and even a third visit. In the moderate grades of hypertension, the second visit should be within a few days, but in mild hypertension it should be within a month or two. If blood pressures are settling a further rechecking visit may be considered worth while. Most of the published clinical trials of the management of hypertension with diastolic pressures of around 100 mmHg have instituted therapy only on the basis of the average of blood pressure readings taken on three separate visits. There is evidence that in many mild hypertensives pressures continue to settle even after this so patients should be monitored for about six months and only if pressures remain raised should drug therapy be introduced.

INVESTIGATIONS IN GENERAL PRACTICE

The investigations recommended and their interpretation are discussed in Chapter 7. Briefly, we suggest that all patients should have their urine tested by a dipstick method. Biochemical and haematological profiles and an ECG should be performed only in patients who are to receive antihypertensive drug therapy, or if there are specific reasons to suspect some associated disease or complication.

BLOOD PRESSURE REDUCTION REGIMES IN GENERAL PRACTICE

The possible schemes for the reduction of blood pressure are discussed in Chapters 10 and 11. There is no basic difference between the drug regimes recommended in primary care and in hospital practice.

- Step 1 Non-pharmacological therapy
- Step 2 Thiazide beta-blocker, calcium-entry antagonist or converting-enzyme inhibitor
- Step 3 Combination of two drugs
- Step 4 Combination of above three drugs.

It is recommended that family doctors should where necessary proceed as far as triple therapy, and this should provide adequate blood pressure control in up to about 80 per cent of cases. Patients whose pressures remain uncontrolled should be referred for specialist consultation and detailed investigation.

HOSPITAL REFERRAL

Each family doctor probably has on his list about ten to fifteen hypertensive patients with clinical problems requiring

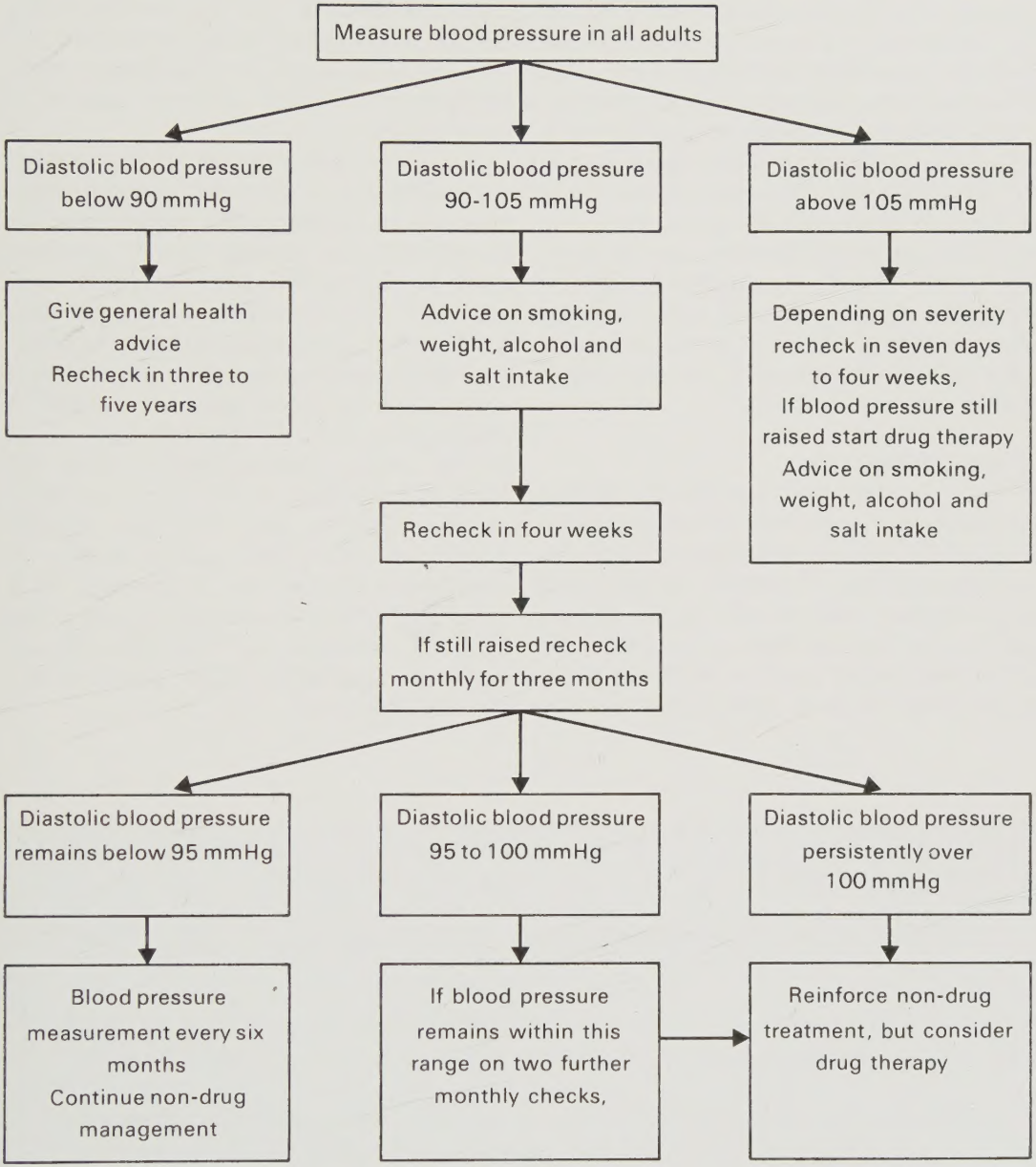

Figure 13.3 Guidelines for the protection and management of mild hypertension: the recommendations of WHO and the International Society for Hypertension (from *J. Hypertension 4*, 1986, 383–6).

referral to a specialist clinic (see Chapter 8). Sometimes a discussion by telephone with the consultant in charge of the local blood pressure clinic may prove sufficient.

The main disadvantage of hospital clinic referral is that it can lead to fragmentation of the patient's care, confusion about changes in drug regimes and an excessive proliferation of paperwork. Furthermore, the family doctor frequently 'loses' his patient to the hospital and feels inhibited from involving himself in clinical care. This can be minimized if the concept of shared care is followed.

SHARED CARE

It is important that the family doctor continues to contribute to the management of the patient throughout treatment for hypertension. If patients are provided with a patient-held record card (see above) the doctor can continue to provide the clinic with blood pressure readings taken at the time of each repeat prescription. Thus the specialist can see that the family doctor is still taking an active interest, and will be encouraged to discontinue clinic attendance if blood pressure control is satisfactory.

A further development of the shared-care principle is that the hospital clinic arranges to discharge the patient but, by six monthly or annual postal questionnaire to the family doctor (usually with the aid of a computer), checks that medical care continues and that the blood pressure is satisfactory. If no information is available or blood pressure control is inadequate, then an appointment is sent to the patient automatically. Thus the hospital continues to receive information on the patient, who may not actually attend for years, and a high quality of continuous clinical care is ensured.[6] It is to be hoped that developments along this line will continue and the efficiency of longterm control of blood pressure will thus be improved.

PRACTICAL POINTS

- Better longterm control of blood pressure is now increasingly common in the US and in some centres in Britain.[7]
- The family doctor, perhaps in collaboration with a local specialist, should attempt to improve efficiency in case detection and follow-up.
- Clinical trials have demonstrated the effectiveness of these manoeuvres in preventing premature heart attacks and strokes.
- The management of hypertension in the community is primarily the responsibility of the practitioner.
- Case detection and follow-up should now be regarded as an integral and routine part of good clinical care.

High blood pressure affects up to 20 per cent of the population in Western societies. It is one of the most preventable causes of heart attack and stroke. Yet a regrettable state of under-diagnosis, under-treatment and poor control persists. Aiming to rectify this, Gareth Beevers and Graham MacGregor, both leading authorities on hypertension, have produced a practical, clinically oriented text specially for general practitioners, but also invaluble for undergraduates, post-graduate trainees and anyone concerned with hypertension in primary care.
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